Abstract and Introduction

Abstract

Objective. In a 3-year randomized, double-blind, osteoporosis treatment study (N = 7,492), bazedoxifene 20 mg and bazedoxifene 40 mg significantly (P < 0.05) reduced the risk of new vertebral fractures by 42% and 37%, respectively, compared with placebo in postmenopausal women with osteoporosis. This study evaluated the long-term (7-y) efficacy and safety of bazedoxifene in generally healthy postmenopausal women with osteoporosis.

Methods. This was a second 2-year extension of the 3-year multicenter outpatient core study. During extension I (years 4-5), women receiving bazedoxifene 40 mg transitioned to bazedoxifene 20 mg. In extension II (years 6-7; N = 1,530), all bazedoxifene-treated women continued bazedoxifene 20 mg. Main outcome measures included year 7 endpoints: incidences of new vertebral and nonvertebral fractures, bone mineral density changes, and safety assessments.

Results. At 7 years, the cumulative incidences of new vertebral fractures were significantly lower in the bazedoxifene (6.4%) and bazedoxifene 20 mg (7.6%) groups than in the placebo group (9.9%); the relative risk reductions were 36.5% and 30.4%, respectively (both P < 0.001). Bazedoxifene had no effect on the overall incidence of nonvertebral fractures (bazedoxifene, 11.2%; bazedoxifene 20 mg, 12.0%; placebo, 10.8%). The mean changes from baseline in lumbar spine bone mineral density were 2.95%, 2.73%, and 2.19%, respectively. Seven-year decreases in total hip bone mineral density were significantly smaller in the bazedoxifene (−1.15%) and bazedoxifene 20 mg (−1.19%) groups than in the placebo group (−2.53%; P ≤ 0.002). Bazedoxifene showed a favorable safety/tolerability profile across 7 years, with similar adverse events, serious adverse events, and study discontinuations in all groups.

Conclusions. Efficacy and safety of bazedoxifene are sustained across 7 years in postmenopausal women with osteoporosis.

Introduction

Osteoporosis disproportionately affects postmenopausal women, in whom declining estrogen production accelerates bone loss.[1-5] Osteoporosis-related fractures cause increased morbidity and mortality, and impose a heavy economic burden.[4-6] Currently available therapies for prevention or treatment of postmenopausal osteoporosis include bisphosphonates, hormone therapy, parathyroid hormone, denosumab, strontium ranelate (outside the United States), and selective estrogen receptor modulators (SERMs).[7] Each is associated with unique benefits and risks. As such, not all currently available therapies are appropriate for long-term use. For example, bisphosphonates are associated with atypical, low-impact subtrochanteric stress fractures, the risk of which increases with duration of therapy.[8-10] Thus, there is a continued need for therapies that are effective in preventing bone loss and in reducing fracture risk and have a favorable long-term safety/tolerability profile.

Bazedoxifene (BZA) is a novel SERM that is available in the European Union, Japan, and Korea for treatment of osteoporosis in postmenopausal women at increased risk for fracture. In a 2-year phase 3 osteoporosis prevention study (N = 1,583), daily oral doses of BZA 10, 20, and 40 mg effectively prevented bone loss in at-risk postmenopausal women. All doses were associated with a favorable safety/tolerability profile and had no adverse effects on the reproductive system.[11,12] In a 3-year multicenter, randomized, double-blind, placebo (PBO)— and active-controlled phase 3 osteoporosis treatment study (N = 7,492) that was the core study (years 1-3) for the 7-year analyses reported here, BZA 20 mg (BZA20) and BZA 40 mg (BZA40) significantly (P < 0.05) reduced the risk of new vertebral fractures by 42% and 37%, respectively, compared with PBO in postmenopausal women with osteoporosis.[13] There was no overall treatment effect on nonvertebral fractures; however, in a post hoc analysis of women at higher risk for fracture (n = 1,772), BZA20 significantly (P ≤ 0.05) reduced the risk of nonvertebral fractures compared with PBO and raloxifene 60 mg (RLX60). A 2-year extension of the core study (extension I) demonstrated that the efficacy of BZA was sustained through 5 years of treatment.[14] BZA did not stimulate the endometrium or breast and was generally safe and well tolerated for 5 years.[13-17] A second 2-year extension (extension II, years 6-7) has been completed. The objective of this report is to describe the efficacy and safety of BZA compared with PBO across 7 years of therapy.

Methods

Participants and Study Design

The methodologies for the core study and for extension I have been reported previously.[13-17] The core study enrolled generally healthy postmenopausal women aged 55 to 85 years with osteoporosis, as determined by low bone mineral density (BMD) or
prevailing vertebral fractures. Women with prevalent vertebral fractures were required to have a lumbar spine or femoral neck BMD \( T \) score of \(-4.0 \) or higher, those without existing vertebral fractures were required to have a lumbar spine BMD \( T \) score of \(-2.5 \) or lower or a femoral neck BMD \( T \) score of \(-4.0 \) or higher.

Women who completed extension I and signed a new written informed consent form were eligible for extension II. Extension II exclusion criteria included a history of venous thromboembolic events (VTEs), stroke, or transient ischemic attack, or any disease or abnormal physical finding that would preclude participation. During extension II, women who experienced a new vertebral fracture or a \( 7\% \) or higher decrease from baseline in lumbar spine or hip BMD remained in the study and were prescribed bisphosphonates or calcitonin. In contrast, in the core study, women with new vertebral fractures or low BMD were withdrawn.

In the core study, women were randomized to receive daily oral BZA20, BZA40, RLX60, or PBO. All women received up to 1,200 mg/day elemental calcium and up to 800 IU/day vitamin D. During extension I, the RLX60 arm was discontinued after the 3-year database was finalized, and women receiving BZA40 were transitioned to BZA20 after the last participant completed 4 years of treatment. All women who entered extension II on active treatment continued to receive BZA20. Seven-year efficacy was determined for all women who received BZA during the study, for women who received only BZA20 throughout 7 years, and for those given PBO. Safety data at 7 years are reported for all BZA-treated and PBO-treated women.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol, written informed consent form, and subsequent amendments or revisions to either document were reviewed and approved by the institutional review board or an independent ethics committee in each institution.

**Efficacy Criteria**

The primary efficacy endpoint was the incidence of new radiographically confirmed vertebral fractures after 84 months. Secondary efficacy endpoints included the incidences of clinical vertebral fractures, worsening vertebral fractures, and nonvertebral fractures, and changes from baseline in spine, hip, and femoral BMD. The incidence of new vertebral fractures was assessed via thoracic and lumbar (T4-L4) radiographs at the end of extension I (month 60) and during extension II (months 72 and 84). Assessment of vertebral fractures was performed in blinded fashion at a central radiographic facility (Synarc, San Francisco, CA) using a semiquantitative method.[18] New incident vertebral fractures were confirmed by quantitative morphometric assessment, with incident fractures defined as a \( 20\% \) or higher decrease or a 4-mm or higher decrease in vertebral height. In cases of disagreement between the two assessments, an independent reader confirmed or refuted the presence of a new vertebral fracture using the semiquantitative method. At each clinic visit, women were questioned about the occurrence of nonvertebral fractures; every effort was made to verify fracture diagnoses.

**Safety Criteria**

Safety and tolerability were evaluated by adverse event (AE) reporting, physical and gynecologic examinations, and clinical laboratory determinations. AEs of special interest (breast cancer, VTEs, and cerebrovascular events) were evaluated by blinded independent adjudication boards in the core study and in both extensions.

**Statistical Methods**

New vertebral fractures were assessed in all randomized women who received one or more doses of study medication and had a baseline assessment and one or more postbaseline assessments (modified intent-to-treat [MITT]) Nonvertebral fractures were assessed in all women who received one or more doses of study medication and in a higher-risk population comprising women who had a femoral neck \( T \) score of \(-3.0 \) or lower or one or more moderate vertebral fractures or multiple vertebral fractures at baseline. BMD was evaluated in the extension II MITT population (ie, all women who received \( \geq 1 \) dose of study medication in extension II and had a baseline assessment and one or more assessments during extension II).

Cumulative fracture rates through 84 months were calculated using Kaplan-Meier estimates and 95% CIs. Cumulative fracture rates between groups were compared by stratified log-rank test, using baseline vertebral fracture status for stratification. Cox regression was used to estimate hazard ratios (HRs) and 95% CIs for each time point, with baseline vertebral fracture status and treatment as indicator factors and with baseline BMD \( T \) score as a continuous covariate. A post hoc analysis of the safety population (ie, women receiving \( \geq 1 \) dose of study medication in years 6-7) examined the incidence of new vertebral fractures during extension II in the BZA20 and population). Randomized BZA treatment groups compared with PBO. Percentage change from baseline in BMD was compared at the 0.05 level using an analysis of covariance model that included treatment and baseline vertebral fracture status as factors. Baseline \( T \) score was included as a covariate.

Baseline and demographic characteristics with continuous variables were compared between groups using one-way analysis of variance with treatment as the only factor. Comparisons of categorical variables were performed using \( \chi^2 \) test. Between-group differences in AEs were analyzed using \( \chi^2 \) test or Fisher's exact test.

**Results**

Participant disposition through the core study and extensions is shown in Figure 1. Extension II enrolled 1,732 women; 1,301 completed extension II (23% and 85% of dosed women in the core study and in extension II, respectively), and 1,530 received one or more doses of study medication and were included in the safety population. The baseline and demographic characteristics of extension II participants were similar to those of the overall study population, with no significant differences between BZA-treated and PBO-treated women ( ).

**Table 1. Baseline and demographic characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall study population</th>
<th>Extension II study population</th>
</tr>
</thead>
</table>
Age, mean (SD), y  
BZA (n = 3,758) 66.4 (6.7)  
BZA 20 mg (n = 1,886) 66.5 (6.5)  
PBO (n = 1,885) 66.5 (6.8)  
BZA (n = 1,011) 65.7 (6.2)  
PBO (n = 519) 65.7 (6.1)  

Race, n (%)  
White 3,280 (87.3)  
BZA 20 mg (n = 1,886) 1,657 (87.9)  
PBO (n = 1,885) 1,641 (87.1)  
BZA (n = 1,011) 852 (84.3)  
PBO (n = 519) 442 (85.2)  
Black 250 (6.7)  
BZA 20 mg (n = 1,886) 115 (6.1)  
PBO (n = 1,885) 120 (6.4)  
BZA (n = 1,011) 86 (8.5)  
PBO (n = 519) 37 (7.1)  
Hispanic 173 (4.6)  
BZA 20 mg (n = 1,886) 90 (4.8)  
PBO (n = 1,885) 88 (4.7)  
BZA (n = 1,011) 57 (5.6)  
PBO (n = 519) 27 (5.2)  
Other 55 (1.5)  
BZA 20 mg (n = 1,886) 24 (1.3)  
PBO (n = 1,885) 36 (1.9)  
BZA (n = 1,011) 16 (1.6)  
PBO (n = 519) 13 (2.5)  

Time since LMP, mean (SD), y  
BZA (n = 3,758) 19.5 (8.7)  
BZA 20 mg (n = 1,886) 19.7 (8.6)  
PBO (n = 1,885) 19.5 (8.8)  
BZA (n = 1,011) 18.7 (7.8)  
PBO (n = 519) 18.2 (8.0)  

Natural menopause, n (%)  
BZA (n = 3,396) 3,396 (90.4)  
BZA 20 mg (n = 1,706) 1,706 (90.5)  
PBO (n = 1,738) 1,738 (92.2)  
BZA (n = 933) 933 (92.3)  
PBO (n = 491) 491 (94.6)  

BMI, mean (SD), kg/m^2  
BZA (n = 1,011) 26.5 (3.8)  
BZA 20 mg (n = 1,011) 26.6 (3.8)  
PBO (n = 519) 26.3 (3.8)  

BMD T score, mean (SD)  
Lumbar spine ND  
BZA (n = 1,011) ND  
PBO (n = 519) ND  
Femoral neck ND  
BZA (n = 1,011) ND  
PBO (n = 519) ND  
Total hip ND  
BZA (n = 1,011) ND  
PBO (n = 519) ND  

Prevalent vertebral fractures, n/N (%)  
BZA (n = 1,909) 1,909/3,410 (56.0)  
BZA 20 mg (n = 967) 967/1,724 (56.1)  
PBO (n = 981) 981/1,741 (56.4)  
BZA (n = 522) 522/1,032 (50.6)  
PBO (n = 272) 272/535 (50.8)  

25(OH)D, mean (SD), nmol/L  
BZA (n = 1,011) 61.4 (22.7)  
BZA 20 mg (n = 1,011) 60.8 (23.5)  
PBO (n = 519) 60.9 (22.8)  

BZA, bazedoxifene; PBO, placebo; LMP, last menstrual period; BMI, body mass index; BMD, bone mineral density; ND, not determined; 25(OH)D, 25-hydroxyvitamin D.  

a Percentages may not total 100.0% because of rounding.  
b Includes Asian, Native American, and other ethnic origins.  
c P < 0.05 versus PBO (χ² test).  
d P < 0.05 versus PBO (one-way analysis of variance with treatment as factor).  
e Data for the modified intent-to-treat population are for BMD analysis only.  
f Data for the modified intent-to-treat population are for vertebral fracture analysis only.
Flow chart of women throughout the core study and extensions. Randomized and received ≥1 does of study drug (n = 7,492) is the sum of the 4 original treatment arms and will not match the sum of the 3 arms in this study. BZA, bazedoxifene; PBO, placebo. a Excludes observational substudy women who discontinued during extension II and 31 women who did not enter extension II and had inaccurate termination records. b Does not account for all deaths reported to sponsor. Overall P < 0.05.

The mean compliance rate (ie, percentage of scheduled medication capsules consumed) across 7 years was 94.8%, 94.9%, and 95.1% for the BZA, BZA20, and PBO groups, respectively. Compliance for years 6 to 7 was 95.0%, 94.9%, and 95.9%, respectively. During extension II, a significantly (P < 0.01) higher proportion of PBO-treated women (18.6%) used concomitant bone-active nonstudy medications compared with the BZA (11.7%) and BZA20 (11.8%) groups.

Vertebral Fractures

The cumulative rate of new radiographically confirmed vertebral fractures (Kaplan-Meier estimate) at 7 years was significantly lower for the BZA (6.4%) and BZA20 (7.6%) groups than for the PBO group (9.9%; Figure 2A), corresponding to relative risk reductions of 36.5% and 30.4%, respectively (Figure 2B). Estimated cumulative rates of new vertebral fractures were similar when women who received bone-active nonstudy medications (BZA, n = 180; BZA20, n = 90; PBO, n = 128) were excluded (6.5%, 7.7%, and 10.1%, respectively; P < 0.001 for BZA and P < 0.05 for BZA20 vs PBO).

Kaplan-Meier estimates of new vertebral fracture rates (A) and cumulative incidence of new vertebral fractures (B) at 7 years in the modified intent-to-treat population. BZA, bazedoxifene; PBO, placebo; RRR, relative risk reduction; HR, hazard ratio. a Log rank P < 0.05 for BZA and BZA 20 mg versus PBO.

The Kaplan-Meier cumulative rate estimate of new clinical vertebral fractures was 1.28% (95% CI, 0.82-1.97) in the BZA group and 1.92% (95% CI, 1.20-3.08) in the PBO group across 7 years (P = 0.18). Seven women (0.21%) in the BZA group and 1 woman (0.06%) in the PBO group had worsening vertebral fractures; these low numbers were insufficient for a definitive statistical comparison.

Among women with prevalent vertebral fractures at baseline, BZA significantly reduced the cumulative rate of new vertebral fractures compared with PBO (BZA, 6.9%; BZA20, 8.3%; PBO, 11.4%). The relative risk reductions were 39.0% (HR, 0.61; 95% CI, 0.43-0.86; P = 0.004) for the BZA group and 32.6% (HR, 0.67; 95% CI, 0.45-1.00; P = 0.048) for the BZA20 group. Among women with no prevalent fractures at baseline, the BZA and BZA20 groups had nonsignificant reductions in the incidence of vertebral fractures compared with PBO (5.8%, 6.8%, and 8.2%, respectively), corresponding to PBO (5.8%, 6.8%, and 8.2%, respectively), corresponding to 1.05) and 26.2% (HR, 0.74; 95% CI, 0.44-1.23).

The absolute numbers of women who developed new vertebral fractures during extension II were 20 of 1,032, 14 of 506, and 15 of 535 for the BZA, BZA20, and PBO groups (Kaplan-Meier rate estimates of 2.4%, 3.4%, and 3.4%, respectively). The BZA group showed a 32.6% statistically insignificant relative risk reduction for years 6 to 7 compared with PBO (HR, 0.67; 95% CI, 0.35-1.32); the rate for BZA20 was similar to that for PBO (relative risk reduction, 2.7%; HR, 0.97; 95% CI, 0.47-2.02).

Nonvertebral Fractures

Within the overall safety population, the cumulative incidence of nonvertebral fractures was similar among treatment groups (Kaplan-Meier rate estimates: BZA, 11.2%; BZA20, 12.0%; PBO, 10.8%). In the higher-risk subset (n = 1,324), the cumulative rate of nonvertebral fractures was numerically, but not significantly, lower for the BZA (12.8%; HR, 0.72; 95% CI, 0.48-1.07) and BZA20 (12.8%; HR, 0.68; 95% CI, 0.42-1.10) groups.
Bone Mineral Density

At 7 years, all groups showed significant increases in adjusted mean (SE) percentage changes from baseline in lumbar spine BMD: BZA, 2.95% (0.39%); BZA20, 2.73% (0.51%); PBO, 2.19% (0.49%) (P < 0.001 vs baseline for all; Figure 3A). Increases from baseline to year 7 in lumbar spine BMD were greater for the BZA and BZA20 groups than for PBO, but these differences were not statistically significant. On year 6, the BZA and BZA20 groups also showed greater, but not statistically significant, mean (SE) increases from baseline in lumbar spine BMD compared with PBO: 2.24% (0.31%), 1.92% (0.41%), and 1.80% (0.40%), respectively.

Figure 3. Changes in bone mineral density at the lumbar spine (A) and total hip (B) across 7 years. Bone mineral densities at the lumbar spine and total hip were measured by dual-energy x-ray absorptiometry at the end of extension I and on months 72 and 84 during extension II. All dual-energy x-ray absorptiometry measurements were evaluated at a central facility (Synarc, San Francisco, CA). BZA, bazedoxifene; PBO, placebo. For (A) P < 0.01 versus PBO for BZA and BZA 20 mg at all time points, except for months 60, 72, and 84. For (B) P < 0.001 versus PBO for BZA and BZA 20 mg at all time points.

All groups showed statistically significant decreases from baseline in total hip BMD at 7 years: adjusted mean (SE) percentage changes: BZA, −1.15% (0.30%), P < 0.001; BZA20, −1.19% (0.39%), P = 0.002; PBO, −2.53% (0.38%), P < 0.001 (Figure 3B).

On year 7, compared with PBO, the BZA and BZA20 groups showed significantly smaller BMD reductions from baseline in total hip (both P < 0.001), femoral neck (both P < 0.001), and femoral trochanter (both P < 0.01) assessments. Similar BMD results were seen at all four sites when data from women receiving bone-active nonstudy medications were excluded.

Safety and Tolerability

BZA treatment up to 7 years was associated with a favorable safety/tolerability profile. The incidences of AEs, serious AEs, and AE-related study discontinuations in the overall safety population were similar between the BZA group and the PBO group ( ). The most common AEs (reported by ≥20% of women in at least one group) were abdominal pain, accidental injury, back pain, flu syndrome, headache, infection, pain, hypertension, constipation, and arthralgia. Compared with PBO, the BZA group showed higher incidences of hot flushes (13.3% vs 6.7%; P < 0.001) and leg cramps (14.1% vs 10.8%; P < 0.001) across 7 years. Hot flush incidence was highest during the first year of BZA and steadily decreased (129.4, 28.9, 9.6, 7.8, 10.1, 6.0, and 2.3 per 1,000 woman-years for years 1-7, respectively). Leg cramp incidence was highest during the first year, decreased through year 3, and leveled off (99.8, 40.5, 21.8, 30.8, 20.2, 33.6, and 13.9 per 1,000 woman-years for years 1-7). Similar trends were observed for the incidences of hot flushes and leg cramps with PBO. Safety findings for years 6 to 7 (extension II safety population) were similar to those observed across 7 years. BZA was not associated with increased incidences of ischemic cardiac disorders across 7 years or during extension II ( ). There were no significant differences in the incidence of cerebrovascular events (HR, 1.06; 95% CI, 0.62-1.81) between the BZA group and the PBO group. Incidence of VTE was higher in the BZA group compared with the PBO group (HR, 1.62; 95% CI, 0.8-3.3) owing to a higher incidence of deep vein thrombosis (DVT; HR, 3.38; 95% CI, 1.01-11.39; P < 0.05). This finding is similar to that observed at 5 years.17 The incidence of DVT was highest during the first year (2.9 per 1,000 woman-years), with lower rates in subsequent years (1.4, 1.2, 1.0, and 0.6 for years 2-5) and no new cases during years 6 and 7. The overall HR for VTEs remained similar at 3 years (HR, 1.66; 95% CI, 0.75-3.66), 5 years (HR, 1.57; 95% CI, 0.77-3.21), and 7 years (HR, 1.62; 95% CI, 0.8-3.3).

Table 2. Summary of safety profile.

<table>
<thead>
<tr>
<th>Overall safety population</th>
<th>Safety population of Extension II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years 0-7</td>
</tr>
<tr>
<td></td>
<td>BZA (n = 3,758)</td>
</tr>
<tr>
<td></td>
<td>PBO (n = 1,885)</td>
</tr>
<tr>
<td>Any AE</td>
<td>3,634 (96.7)</td>
</tr>
<tr>
<td></td>
<td>1,830 (97.1)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>975 (25.9)</td>
</tr>
<tr>
<td></td>
<td>479 (25.4)</td>
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### Table 2. Summary of safety profile.

<table>
<thead>
<tr>
<th>Selected AEs</th>
<th>Overall safety population</th>
<th>Safety population of Extension II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years 0-7</td>
<td>Years 6-7</td>
</tr>
<tr>
<td></td>
<td>BZA (n = 3,758)</td>
<td>PBO (n = 1,885)</td>
</tr>
<tr>
<td></td>
<td>BZA (n = 1,091)</td>
<td>PBO (n = 561)</td>
</tr>
<tr>
<td>Discontinuations because of AEs</td>
<td>691 (18.4)</td>
<td>323 (17.1)</td>
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<tr>
<td></td>
<td>29 (2.7)</td>
<td>14 (2.5)</td>
</tr>
<tr>
<td>Death</td>
<td>52 (1.4)</td>
<td>18 (1.0)</td>
</tr>
<tr>
<td></td>
<td>10 (0.9)</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Coronary occlusion</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>27 (0.7)</td>
<td>13 (0.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22 (0.6)</td>
<td>12 (0.6)</td>
</tr>
<tr>
<td>Total stroke, b</td>
<td>42 (1.1) [2.9; 2.1-3.9]</td>
<td>20 (1.1) [2.7; 1.7-4.2]</td>
</tr>
<tr>
<td>Ischemic</td>
<td>28 (0.7) [1.9; 1.3-2.8]</td>
<td>13 (0.7) [1.8; 1.0-3.0]</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5 (0.1) [0.4; 0.1-0.8]</td>
<td>5 (0.3) [0.7; 0.2-1.6]</td>
</tr>
<tr>
<td>Unspecified</td>
<td>9 (0.2) [0.6; 0.3-1.2]</td>
<td>2 (0.1) [0.3; 0.03-1.0]</td>
</tr>
<tr>
<td>TIA, b</td>
<td>19 (0.5) [1.3; 0.8-2.1]</td>
<td>4 (0.2) [0.6; 0.2-1.4]</td>
</tr>
<tr>
<td>VTE, b, c</td>
<td>32 (0.9) [2.2; 1.5-3.1]</td>
<td>10 (0.5) [1.4; 0.7-2.5]</td>
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<tr>
<td>Deep vein thrombosis</td>
<td>20 (0.5) [1.4; 0.8-2.1]</td>
<td>3 (0.2) [0.4; 0.1-1.2]</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>7 (0.2) [0.5; 0.2-1.0]</td>
<td>4 (0.2) [0.6; 0.2-1.4]</td>
</tr>
<tr>
<td>Retinal vein thrombosis</td>
<td>4 (0.1) [0.3; 0.1-0.7]</td>
<td>3 (0.2) [0.4; 0.1-1.2]</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>23 (0.6)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Breast cyst</td>
<td>22 (0.6)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Fibrocystic breast disease</td>
<td>19 (0.5)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>112 (3.0)</td>
<td>52 (2.8)</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>3 (0.1)</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Uterine hemorrhage</td>
<td>10 (0.3)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Vaginal hemorrhage</td>
<td>45 (1.2)</td>
<td>28 (1.5)</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>6 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>500 (13.3)</td>
<td>127 (6.7)</td>
</tr>
<tr>
<td>Leg cramps</td>
<td>531 (14.1)</td>
<td>204 (10.8)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) [95% CI].

BZA, bazedoxifene; PBO, placebo; AE, adverse event; ND, not determined; TIA, transient ischemic attack; VTE, venous thromboembolic event.

a Adjudicated data.

b Rate per 1,000 woman-years.

c Women could have reported more than one category of VTE.

d Adjudication included VTEs other than deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.

P < 0.05 versus PBO (Fisher’s exact test).

P < 0.001 versus PBO (Fisher’s exact test).
decreases in total hip BMD were seen at 5 years contributed to this increase. Although the core study showed a significant increase in total hip BMD with BZA at 3 years, the increase in lumbar spine BMD observed in the PBO group starting on year 5. Calcium and vitamin D supplementation may have greater, but not statistically significantly, in the BZA group than in the PBO group; however, statistical power was limited by the significant improvements from baseline in lumbar spine BMD with BZA and PBO at 7 years. The increase was assessed using the Fracture Risk Assessment Tool.

They are also consistent with results from an independent reanalysis of data from the core study, in which BZA had a greater treatment effect on women with increasing fracture probability, as reductions in the risk of nonvertebral fractures at 7 years (BZA, 28%; BZA20, 32%) versus PBO, but they were not statistically significant. These trends are consistent with findings at 3 years showing a significant reduction in the risk of nonvertebral fractures among higher-risk women treated with BZA.20 At 7 years and during extension II, the incidences of breast carcinoma and other breast-related AEs were low and similar between the BZA group and the PBO group. There were no between-group differences in the overall incidence of endometrial hyperplasia and no new cases during years 6 to 7. The overall incidence of endometrial carcinoma was significantly lower in the BZA group than in the PBO group (0.1% and 0.4%, respectively; P = 0.02); no cases of endometrial carcinoma were reported with BZA20 (P = 0.008 vs PBO). During years 6 to 7, there were no new cases of endometrial carcinoma in the BZA group and one case of endometrial carcinoma in the PBO group. There was a numerical, but not statistically significant, difference in the incidence of ovarian carcinoma (BZA, 0.2%; PBO, 0.0%) across 7 years (P = 0.19); no new cases were reported during years 6 and 7.

Discussion

The overall findings for 7 years of BZA treatment are consistent with those at 3 and 5 years.13-17 We observed significant reductions in the relative risks of new vertebral fractures through 7 years (BZA, 36.5%; BZA20, 30.4%), comparable to findings reported for RLX60 and raloxifene 120 mg (36% and 43%, respectively) after 4 years.19 During extension II, the BZA group had a 32.6% relative risk reduction in the rate of new vertebral fractures.

BZA had no effect on the incidence of nonvertebral fractures at 3, 5, or 7 years.13,14 In a higher-risk subpopulation, there were reductions in the risk of nonvertebral fracture at 7 years (BZA, 28%; BZA20, 32%) versus PBO, but they were not statistically significant. These trends are consistent with findings at 3 years showing a significant reduction in the risk of nonvertebral fractures among higher-risk women treated with BZA20.13 They are also consistent with results from an independent reanalysis of data from the core study in which BZA had a greater treatment effect on women with increasing fracture probability, as assessed using the Fracture Risk Assessment Tool.20,21

Significant improvements from baseline in lumbar spine BMD were seen with BZA and PBO at 7 years. The increase was greater, but not statistically significantly, in the BZA group than in the PBO group; however, statistical power was limited by the increase in lumbar spine BMD observed in the PBO group starting on year 5. Calcium and vitamin D supplementation may have contributed to this increase. Although the core study showed a significant increase in total hip BMD with BZA at 3 years,13
decreases in total hip BMD were seen at 5 years \[14\] and 7 years in all groups. Reductions in hip BMD at 5 and 7 years were significantly smaller in the BZA groups than in the PBO group. The difference in the change in total hip BMD between BZA and PBO was approximately 1% at 5, 7, and 7 years.\[13,14\]

The significant difference in vertebral fracture incidence, but not changes in BMD, observed with BZA (compared with PBO) at 7 years suggests that factors independent of BMD may contribute to fracture risk reduction. Reductions in bone turnover and/or improvements in bone properties/microarchitecture have been linked to enhanced bone strength with other osteoporosis treatments (eg, risedronate and alendronate).\[22-29\] Significant reductions in bone turnover markers were seen in the core study \[13\] and were still apparent in the BZA groups after 5 years.\[14\]

**Conclusions**

BZA treatment was safe and well tolerated, with no increase in the risk of ischemic cardiac disorders or stroke across 7 years, consistent with findings at 3 and 5 years.\[15-17\] BZA was associated with higher incidences of hot flushes and leg cramps across 7 years. Increases in hot flushes and leg cramps have also been reported for 8 years of treatment with raloxifene.\[26-28\] The BZA group also showed higher incidences of VTEs, primarily DVT, compared with PBO. Most DVTs occurred during the core study (HR of 8.7 for years 0-3 vs HR of 3.4 for years 0-5 and years 0-7). No new cases were reported during years 6 to 7, and the overall risk of VTEs was stable across 3, 5, and 7 years. Safety data from years 6 to 7 should be interpreted with caution, as women with a history of VTEs, stroke, or transient ischemic attack were excluded from extension II. Like all SERMs, BZA is contraindicated in women with a history of blood clots. An increased risk of VTEs has been observed for estrogens, tamoxifen, raloxifene, and lasofoxifene.\[28-30\]

BZA treatment showed no evidence of breast or endometrial stimulation. The incidence of endometrial carcinoma was significantly lower in the BZA group compared with the PBO group at 7 years, as at 5 years.\[17\] The incidence of breast carcinoma was low and similar for BZA and PBO at 7 years.

An important strength of this study is the inclusion of a continuous PBO group, along with two active arms, across the 7-year study period. Results are also strengthened by the relatively large number of women on BZA entering the extensions. This study is one of the longest PBO-controlled SERM studies and is the only study to have examined long-term treatment effects on new vertebral fractures. The Continuing Outcomes Relevant to Evista (CORE) trial, a 4-year extension of the 4-year Multiple Outcomes of Raloxifene Evaluation osteoporosis treatment trial, evaluated the long-term effects of raloxifene on breast cancer; new nonvertebral fractures and BMD were also assessed.\[31\] After 8 years, raloxifene had no effect on nonvertebral fracture risk, but increases in BMD with raloxifene relative to PBO were maintained for 7 years. The CORE study differed from the current study in that it included women who did not continue to take study medication, and fracture data were not adjudicated. Because the CORE study was designed as a breast cancer prevention trial, the strength and validity of the skeletal data are limited.

On post hoc analyses, the incidence of new vertebral fractures during years 6 to 7 was similar to those for the BZA20 (3.4%) and PBO (3.4%) groups in the safety population. Nonetheless, the observed decline in vertebral fractures in the MITT population was statistically significant across 7 years, suggesting that the efficacy of BZA is maintained through this period. The primary comparison of study arms by stratified log-rank test compares survival experience stratified by baseline fracture status and should not be construed as a direct comparison of (unstratified) Kaplan-Meier estimates.

A potential limitation of this study is that only 23% of women randomized in the core BZA study completed extension II. Furthermore, women were enrolled in extensions I and II on a self-selected basis and, as suggested in other long-term osteoporosis studies, the baseline characteristics of the extension population may differ from those of the core BZA study.\[32\] This may limit the ability to make comparisons between treatment groups and the ability to relate findings from extension II to findings from the randomized core BZA study population. However, the baseline and demographic characteristics of extension II women did not differ significantly between treatment groups and were generally similar to those of the overall study population. Another potential limitation is that women enrolled in extension II, unlike those enrolled in the core BZA study, were allowed to remain in the study and to take other bone-active medications such as bisphosphonates or calcitonin when they developed new vertebral fractures or low BMD. However, similar results were obtained when only data up to the first use of bone-active nonstudy medications were analyzed.

**Conclusions**

In summary, the efficacy of BZA for the treatment of postmenopausal osteoporosis is sustained across 7 years of use. BZA treatment significantly reduces the incidence of new vertebral fractures and improves lumbar spine BMD across 7 years. BZA is generally safe and well tolerated, with no evidence of endometrial or breast stimulation. No new safety concerns for BZA have been identified during years 6 to 7. Results are consistent with those observed at 3 and 5 years and support the safety and efficacy of BZA for the long-term treatment of osteoporosis in postmenopausal women.

**References**


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