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ORIGINAL ARTICLE

Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial

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Abstract
Summary Findings from this 5-year phase 3 study of postmenopausal women with osteoporosis showed that bazedoxifene was associated with an overall favorable safety and tolerability profile, with no evidence of endometrial or breast stimulation. Overall, the results at 5 years were consistent with those seen at 3 years.

Introduction We report safety and tolerability findings from a 5-year randomized, double-blind, phase 3 study of bazedoxifene in postmenopausal women with osteoporosis.
Methods In the core study, healthy postmenopausal women with osteoporosis (N=7,492; mean age, 66.4 years) were randomized to daily doses of bazedoxifene 20 or 40 mg, raloxifene 60 mg, or placebo for 3 years. During the 2-year study extension, the raloxifene 60-mg treatment arm was discontinued after the 3-year database was finalized, and subjects receiving bazedoxifene 40 mg were transitioned in a blinded manner to bazedoxifene 20 mg (bazedoxifene 40-/20-mg group) after 4 years. Safety and tolerability data are reported for subjects in the bazedoxifene 20- and 40-/20-mg and placebo groups; efficacy findings are reported elsewhere.
Results A total of 3,146 subjects in the bazedoxifene 20- and 40-mg and placebo groups were enrolled in the extension study (years 4 and 5). Overall, the 5-year incidence of adverse events (AEs), serious AEs, and discontinuations due to AEs were similar among groups. The incidence of hot flushes and leg cramps was higher with bazedoxifene compared with placebo. Venous thromboembolic events, primarily deep vein thrombosis, were more frequently reported in the bazedoxifene groups compared with the placebo group. Reports of cardiac disorders and cerebrovascular events were few and evenly distributed among groups. Bazedoxifene showed a neutral effect on the breast and endometrium.
Conclusion Bazedoxifene was associated with an overall favorable safety and tolerability profile in postmenopausal women with osteoporosis over 5 years of therapy, consistent with findings at 3 years.

Keywords Bazedoxifene · Osteoporosis · Postmenopausal · Safety · SERMs · Tolerability

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Introduction

Osteoporosis, a skeletal disease of diminished bone strength and increased fracture risk, is characterized by decreased bone mineral density (BMD) and microarchitectural deterioration [1, 2]. Postmenopausal women are at increased risk for fracture as the production of ovarian estrogens ceases after menopause [3]. Osteoporotic fractures are associated with substantial morbidity and mortality and can have a significant impact on health care costs and the patient's quality of life [4, 5]. Numerous agents for the prevention and/or treatment of postmenopausal osteoporosis are currently available, including bisphosphonates, estrogen therapy, parathyroid hormone (PTH), calcitonin, strontium ranelate (outside the USA and Canada), and the selective estrogen receptor modulator (SERM) raloxifene [1]. Although existing pharmacologic agents for postmenopausal osteoporosis have been shown to be effective [6], they may not be appropriate for all women, primarily because of safety or tolerability concerns [7].

A number of novel SERMs are under clinical investigation for the prevention and/or treatment of postmenopausal osteoporosis [8]. SERMs confer mixed estrogen receptor (ER) agonist or antagonist activity depending on the target tissue [9]. There are several "class effects" that are commonly observed with SERMs, including an increased incidence of hot flushes [8, 10–12] and venous thromboembolic events (VTEs) [13–15]. Raloxifene has also been associated with an increased risk of fatality due to stroke, although the overall risk of stroke has not been shown to be significantly different compared with placebo [13].

Bazedoxifene is a novel SERM in late-stage development for the prevention and treatment of postmenopausal osteoporosis. In a 2-year, phase 3 study [16, 17] of postmenopausal women at risk for osteoporosis (N= 1,583), bazedoxifene 10, 20, and 40 mg were shown to prevent bone loss and to reduce bone turnover, with a favorable endometrial, ovarian, and breast safety profile. In a 3-year pivotal, global phase 3 study [18] of postmenopausal women with osteoporosis (N=7,492), bazedoxifene 20 and 40 mg were shown to significantly reduce the risk of new vertebral fracture relative to placebo; in a subgroup of higher-risk women (n=1,772), bazedoxifene 20 mg significantly decreased the risk of nonvertebral fracture compared with both placebo and raloxifene 60 mg. Both doses of bazedoxifene were generally safe and well tolerated and showed no evidence of endometrial or breast stimulation [18, 19]. Many of the subjects completing the 3-year core study chose to participate in a 2-year extension study, in which extended treatment with bazedoxifene showed sustained efficacy in preventing fractures over 5 years of therapy [20]. Herein, we describe the results of safety-related endpoints from the extension study; we hypothesized that, consistent with findings at 3 years, bazedoxifene would be associated with a favorable safety and tolerability profile over 5 years of therapy.

Methods

Study design and subjects

The core study was a 3-year multicenter, randomized, double-blind, placebo- and active-controlled phase 3 trial [18] conducted at 206 sites worldwide and was followed by two 2-year extensions (second 2-year extension is ongoing). Subjects were randomly assigned to receive once-daily oral doses of bazedoxifene 20 or 40 mg, raloxifene 60 mg, or placebo for 3 years. All subjects received oral daily elemental calcium (up to 1,200 mg) and vitamin D (400–800 IU) supplementation. Subjects who were enrolled in the 3-year core study were generally healthy postmenopausal women aged 55 to 85 years with 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 a prevalent vertebral fracture (at least one mild vertebral fracture) were required to have lumbar spine or femoral neck BMD T-scores not worse than −4.0.

A complete description of the inclusion and exclusion criteria for the core study has been published previously [18]. Exclusion criteria included diseases that may affect bone metabolism or conditions that could interfere with measurement of BMD, pathologic vertebral fractures, vasomotor symptoms requiring treatment, active or past history of VTEs, endometrial hyperplasia or carcinoma, abnormal vaginal bleeding, or malignancy within 10 years of the study. Subjects were prohibited from the use of androgens, systemic estrogens (except estriol ≤2.0 mg/day), topical estrogens (>3 times/week), progestogens, SERMs, bisphosphonates, calcitonin, PTH, and cholecalciferol (>50,000 IU/week) within 6 months of screening.

During the extension study, investigators were instructed to prescribe a bisphosphonate or calcitonin (in cases of poor tolerance to bisphosphonates) to subjects experiencing a 7% or greater decrease from baseline in BMD at the lumbar spine or hip or at least one osteoporosis-related fracture (confirmed by a dual X-ray absorptiometry scan or X-ray, respectively) based on the protocol.

Subjects in the raloxifene 60-mg treatment arm were discontinued after all subjects completed 3 years of treatment and the database for the 3-year core study was finalized. Those subjects receiving bazedoxifene 40 mg were transitioned to bazedoxifene 20 mg (bazedoxifene 40-/20-mg group) after all subjects completed 4 years of

treatment. All treatment groups remained blinded throughout the study. The safety data reported herein are for the bazedoxifene 20-mg, bazedoxifene 40/20-mg, and placebo groups. 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. All subjects who were willing to participate in the study extension provided written informed consent at or prior to their visit at month 36. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Assessments

Safety and tolerability were assessed based on physical examinations, gynecologic and breast examinations, mammography, cervical cytology smears, clinical laboratory determinations, and adverse event (AE) reporting. During the extension, physical and gynecologic examinations, laboratory safety determinations, and mammography were performed at months 48 and 60 or upon withdrawal from the study (if >9 months had elapsed since the last assessment). In nonhysterectomized women, cervical cytology smear was done at month 48 or upon withdrawal if more than 18 months had elapsed since the last assessment during the study extension. As previously described [19], transvaginal ultrasound (TVU) of the uterus and ovaries and endometrial biopsy was performed for those subjects participating in the endometrial safety substudy at month 60 (or upon withdrawal from the study if at or after month 48). The US Food and Drug Administration's Coding Symbols for Thesaurus of Adverse Reaction Terms were used to classify AEs.

Independent adjudication boards were formed to ensure a consistent, accurate, and unbiased assessment of the following AEs of interest: VTEs, cerebrovascular events (stroke or transient ischemic attack [TIA]), and breast cancer. The adjudication boards were composed of consultant physicians specializing in the fields of internal medicine with expertise in VTEs, cardiology, breast cancer, neurology, and neuroradiology. All adjudication board members reviewed each case independently in a blinded manner. Thereafter, a final decision was determined for each case based on majority or consensus decision, according to the guidance set forth in each of the adjudication board charters.

Statistical analyses

Safety data were analyzed in all subjects who received at least one dose of study medication during the 5-year study. Differences in the incidence of AEs, serious AEs, and discontinuations due to AEs among treatment groups were evaluated using chi-square analysis, with a significance level set at 0.05. The incidence of VTEs and cerebrovascular events based on adjudicated data were expressed as the rate in 1,000 women-years. Hazard ratios (HRs) of treatment versus placebo were calculated using a proportional hazard model without adjustment for possible covariates; corresponding 95% confidence intervals (CIs) were obtained.

Results

Subjects

A total of 7,492 women received ≥1 dose of study medication and were included in the safety population over the 5-year study. Of the 5,083 subjects who completed the 3-year core study, 3,146 subjects in the bazedoxifene 20- and 40-mg and placebo groups were enrolled in a 2-year extension study (Fig. 1). All subjects in the raloxifene 60-mg group who enrolled in the extension (n=1,070) were discontinued after the database for the 3-year core study was finalized, and subjects receiving bazedoxifene 40 mg were transitioned to bazedoxifene 20 mg (bazedoxifene 40-/20-mg group; n=1,041) after 4 years. Baseline characteristics and demographics of subjects who were enrolled in the extension study were not different among treatment groups (Table 1) and were generally similar to those who were originally enrolled in the core study [18]. At the time of enrollment into the core study, the mean age of subjects who continued on to the extension study was 65.9 years, the mean time since last menstrual period was 18.8 years, and the vast majority of women (91.9%) had natural menopause. A total of 2,503 subjects completed years 4 and 5 of the extension study (Fig. 1); there were no significant differences in the percentage of subjects who discontinued from the study among treatment groups. The most common reason for discontinuation was patient request, followed by AEs.

Over 5 years of therapy, the incidences of AEs, serious AEs, and discontinuations due to AEs in the bazedoxifene treatment groups were not different from that seen in the placebo group (Table 2). Fifty-five subjects in the bazedoxifene and placebo groups had deaths that were reported to the sponsor during the 5-year study: bazedoxifene 20 mg, n=24 (1.3%); bazedoxifene 40/20 mg, n=18 (1.0%); placebo, n=13 (0.7%). Although the overall number of deaths during the 5-year study period was greater in the bazedoxifene groups compared with the placebo group, the differences were not statistically significant and were not attributable to any group of related causes. Cause of death was classified into one of four categories: cardiovascular,

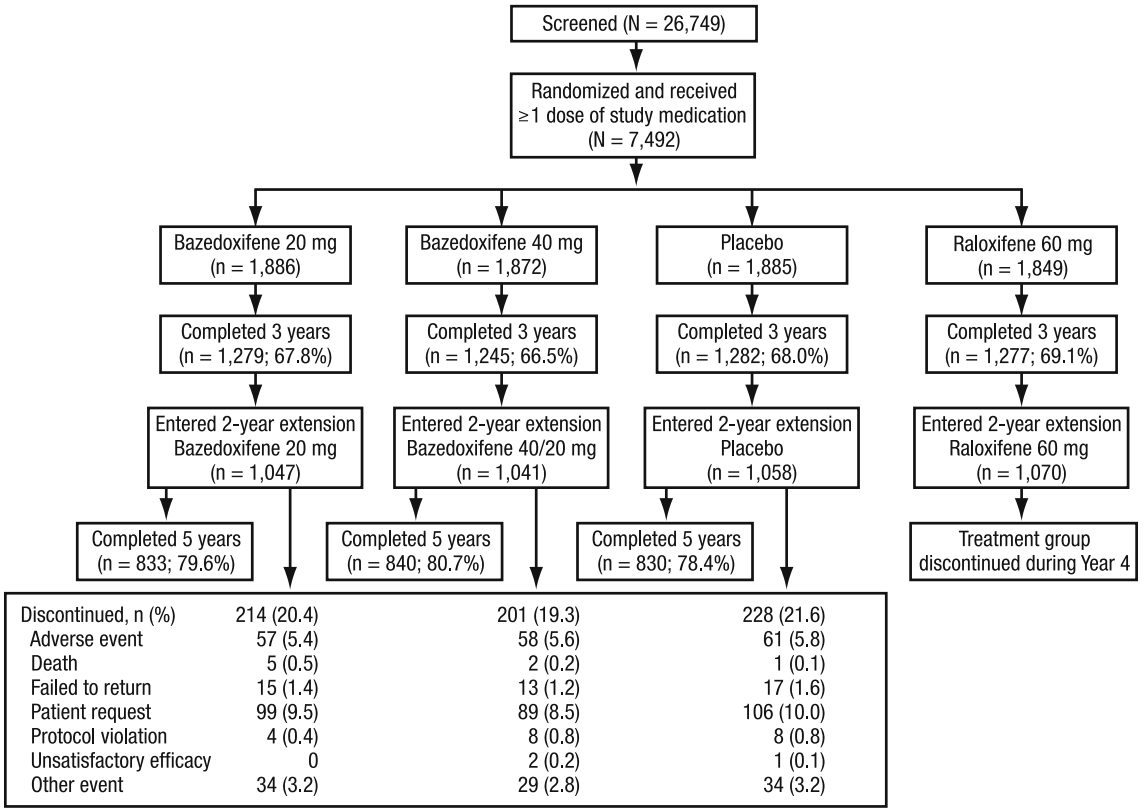

Fig. 1 Subject disposition. The number of subjects who were enrolled, completed, and discontinued the 3-year core study and the 2-year study extension are shown, with reasons for discontinuation provided. The raloxifene treatment arm was discontinued in the fourth year, and subjects receiving bazedoxifene 40 mg were transitioned to bazedoxifene 20 mg after 4 years

oncology, other (which included infection, trauma, upper gastrointestinal bleed, chronic obstructive pulmonary disease, subdural hematoma, myeloproliferative disease, aspiration, postoperative complication, and suicide), and unknown. The numeric imbalance in deaths was due to a greater number of deaths in the categories of oncology and other: for subjects in the bazedoxifene 20- and 40-/20-mg and placebo groups, respectively, there were seven, five, and six deaths in the cardiovascular group; nine, four, and five deaths in the oncology group; six, five, and one death in the "other" group; and two, four, and one death in the "unknown" group. For the oncology-related deaths, there was no specific organ system affected.

The most frequently reported AEs were back pain, arthralgia, pain, flu syndrome, infection, accidental injury, abdominal pain, headache, and hypertension (Table 2). Among AEs reported by >10% of subjects in any treatment group, the incidences of leg cramps and hot flushes were higher in the bazedoxifene treatment groups compared with the placebo group (overall $P<0.01$ and $P<0.001$, respectively). Most reports of leg cramps and hot flushes were mild or moderate in severity and did not result in study discontinuation.

Cardiac disorders

The number of subjects reporting cardiac disorders was low and similar among groups over the 5-year study period. There were no significant differences among the bazedoxifene and placebo groups in the number of subjects reporting coronary occlusion (bazedoxifene 20 mg [$n=2$], bazedoxifene 40/20 mg [$n=1$], placebo [$n=2$]), myocardial infarction (bazedoxifene 20 mg [$n=9$], bazedoxifene 40/20 mg [$n=10$], placebo [$n=11$]), and myocardial ischemia (bazedoxifene 20 mg [$n=12$], bazedoxifene 40/20 mg [$n=13$], placebo [$n=12$]).

Cerebrovascular events

The incidence of cerebrovascular events based on adjudicated data was similar overall among the bazedoxifene and placebo groups over 5 years and was similar to that seen over the first 3 years (Table 3). The rates of total stroke per 1,000 women-years were 2.5 with bazedoxifene 20 mg, 2.7 with bazedoxifene 40/20 mg, and 3.0 with placebo (corresponding HRs [95% CI] of 0.8 [0.4–1.6] and 0.9 [0.5–1.8], respectively; Table 3) over 5 years. There were no significant differences

Table 1 Baseline characteristics and demographics for subjects enrolled in the extension study (years 4 and 5)[a]

Characteristic	Bazedoxifene 20 mg (n=1,047)	Bazedoxifene 40/20 mg (n=1,041)	Placebo (n=1,058)
Age, years			
Mean (SD)	65.9 (6.3)	65.7 (6.4)	65.9 (6.5)
Ethnic origin, n (%)			
White	924 (88.3)	893 (85.8)	921 (87.1)
Black	70 (6.7)	91 (8.7)	72 (6.8)
Hispanic	42 (4.0)	41 (3.9)	43 (4.1)
Other[b]	11 (1.1)	16 (1.5)	22 (2.1)
Years since last menstrual period			
Mean (SD)	19.0 (8.2)	18.7 (8.4)	18.7 (8.5)
Hysterectomy, n (%)	204 (19.5)	214 (20.6)	191 (18.1)
Type of menopause, n (%)			
Natural	965 (92.2)	948 (91.1)	977 (92.3)
Surgical oophorectomy	82 (7.8)	93 (8.9)	81 (7.7)
Hot flushes, n (%)	148 (14.1)	158 (15.2)	136 (12.8)
BMI, kg/m^2			
Mean (SD)	26.5 (3.7)	26.3 (3.9)	26.3 (3.8)
Lumbar spine BMD T-score			
Mean (SD)	−2.4 (1.09)	−2.5 (1.08)	−2.4 (1.08)
Patients with prevalent vertebral fracture, %	54	53	55

SD standard deviation, *BMI* body mass index, *BMD* bone mineral density

[a] Data were collected at baseline of the 3-year core study

[b] Includes Asian, Native American, and other ethnic origins

in the rates of stroke (total, hemorrhagic, ischemic, or unspecified) among treatment groups. Reports of TIA were most frequent in the bazedoxifene 40-/20-mg group (HR [95% CI] of 3.1 [0.99–9.52]; Table 3); the difference relative to placebo was not statistically significant. All cases of TIA were reported in subjects who received bazedoxifene 40 mg before they were transitioned to bazedoxifene 20 mg. There were a total of five fatal strokes over 5 years: bazedoxifene 20 mg (n=2), bazedoxifene 40/20 mg (n=1), and placebo (n=2).

VTEs

A total of 41 VTEs were reported during the 5-year study. The incidence of VTEs (0.7%) based on adjudicated data was higher among subjects treated with bazedoxifene versus placebo over 5 years (Table 4); the differences were not statistically significant. The rates of any VTE per 1,000 women-years were 2.3 with bazedoxifene 20 mg, 2.6 with bazedoxifene 40/20 mg, and 1.6 with placebo (corresponding HRs [95% CI] of 1.5 [0.7–3.4] and 1.7 [0.8–3.6], respectively; Table 4) after 5 years. For clinical perspective, the rate of any VTE per 1,000 women-years for raloxifene 60 mg based on available data was 2.3 (95% CI [1.2–3.9]). The incidence of deep vein thrombosis (DVT) was higher in the bazedoxifene treatment groups compared with the placebo group; the rates per 1,000 women-years were 1.4 with bazedoxifene 20 mg, 1.8 with bazedoxifene 40/20 mg, and 0.5 with placebo (corresponding HRs [95% CI] of 3.0 [0.8–11.1] and 3.8 [1.1–13.5], respectively). Similarly, the rates of superficial thrombophlebitis were higher in the bazedoxifene treatment groups compared with the placebo group. There were no differences in the rates of pulmonary embolism (PE) and retinal vein thrombosis (RVT) among the bazedoxifene and placebo groups.

Breast and reproductive safety

The number of subjects with breast carcinoma was small and evenly distributed among the bazedoxifene 20-mg (n=10), bazedoxifene 40-/20-mg (n=9), and placebo groups (n=10; Table 5). Of these, invasive breast carcinoma was diagnosed in nine subjects in the bazedoxifene 20-mg group, seven subjects in the bazedoxifene 40-/20-mg group, and seven subjects in the placebo group. This included one subject in the bazedoxifene 20-mg group who had a baseline lesion subsequently diagnosed as breast cancer during the study. In addition, there was no significant difference among groups in the number of subjects who had ER-positive breast cancer (bazedoxifene 20 mg [n=4],

Table 2 Summary of safety profile over 5 years

Subjects, *n* (%)	Bazedoxifene 20 mg (*n*=1,886)	Bazedoxifene 40/20 mg (*n*=1,872)	Placebo (*n*=1,885)
Any AE	1,821 (96.6)	1,807 (96.5)	1,826 (96.9)
Any serious AE	467 (24.8)	439 (23.5)	439 (23.3)
Discontinuations due to			
AE	317 (16.8)	325 (17.4)	293 (15.5)
Deaths	24 (1.3)	18 (1.0)	13 (0.7)
AEs >10% in any treatment group			
Back pain	666 (35.3)	640 (34.2)	659 (35.0)
Arthralgia	653 (34.6)	638 (34.1)	643 (34.1)
Pain	620 (32.9)	604 (32.3)	647 (34.3)
Flu syndrome	526 (27.9)	511 (27.3)	547 (29.0)
Infection	514 (27.3)	493 (26.3)	504 (26.7)
Accidental injury*	504 (26.7)	443 (23.7)	527 (28.0)
Abdominal pain	450 (23.9)	449 (24.0)	496 (26.3)
Headache	463 (24.5)	465 (24.8)	463 (24.6)
Hypertension	460 (24.4)	451 (24.1)	452 (24.0)
Constipation	376 (19.9)	367 (19.6)	350 (18.6)
Cough	238 (12.6)	220 (11.8)	225 (11.9)
Leg cramps*	256 (13.6)	249 (13.3)	192 (10.2)
Asthenia	230 (12.2)	220 (11.8)	223 (11.8)
Hot flushes**	245 (13.0)	251 (13.4)	124 (6.6)
Peripheral edema	226 (12.0)	205 (11.0)	185 (9.8)
Diarrhea	189 (10.0)	229 (12.2)	210 (11.1)
Dizziness	223 (11.8)	190 (10.1)	212 (11.2)
Urinary tract infection	219 (11.6)	203 (10.8)	199 (10.6)
Dyspepsia	206 (10.9)	191 (10.2)	216 (11.5)
Bronchitis	200 (10.6)	213 (11.4)	187 (9.9)
Hypercholesteremia**	196 (10.4)	152 (8.1)	224 (11.9)
Arthrosis	185 (9.8)	194 (10.4)	191 (10.1)
Insomnia	190 (10.1)	172 (9.2)	199 (10.6)
Pharyngitis	166 (8.8)	179 (9.6)	205 (10.9)
Select AEs			
Cataract, specified	112 (5.9)	108 (5.8)	113 (6.0)
Cataract, nonspecified	0	1 (0.1)	1 (0.1)

AE adverse event

*$P<0.01$ (chi-square test); **$P<0.001$ (chi-square test)

bazedoxifene 40/20 mg [*n*=3], placebo [*n*=5]). The incidence of breast cyst or fibrocystic breast disease was not significantly different among treatment groups, although there were fewer cases with bazedoxifene 20 and 40/20 mg compared with placebo. The incidence of breast pain was not significantly different among the bazedoxifene and placebo groups.

The incidence of endometrial hyperplasia and neoplasia (polyps) over 5 years was low and evenly distributed among groups. Fewer cases of endometrial carcinoma (overall $P=0.05$) were reported with bazedoxifene 20 mg (*n*=0) and bazedoxifene 40/20 mg (*n*=3) compared with placebo (*n*=6). TVU data were available for 176 subjects at baseline and at year 5 (bazedoxifene 20 mg, *n*=60; bazedoxifene 40/20 mg, *n*=58; placebo, *n*=58). The mean change (± standard error) from baseline in endometrial thickness with bazedoxifene 20 mg (−0.04 ±0.13 mm) and bazedoxifene 40/20 mg (0.07±0.13 mm) was not significantly different from that seen with placebo (−0.19±0.13 mm) at 5 years. The number of subjects with endometrial thickness >5 mm at 5 years was small and similar among the bazedoxifene 20-mg (*n*=0), bazedoxifene 40-/20-mg (*n*=2), and placebo (*n*=0) groups.

Table 3 Rate and hazard ratio of cerebrovascular events over 5 years[a]

	Bazedoxifene 20 mg (n=1,886)	Bazedoxifene 40/20 mg (n=1,872)	Placebo (n=1,885)
Stroke (total)			
n (%)	16 (0.8)	17 (0.9)	19 (1.0)
Rate per 1,000 women-years (95% CI)	2.5 (1.4–4.1)	2.7 (1.6–4.3)	3.0 (1.8–4.6)
HR (95% CI)	0.8 (0.43–1.63)	0.9 (0.48–1.77)	
Hemorrhagic			
n (%)	1 (0.1)	1 (0.1)	4 (0.2)
Rate per 1,000 women-years (95% CI)	0.2 (0.0–0.9)	0.2 (0.0–0.9)	0.6 (0.2–1.6)
HR (95% CI)	0.3 (0.03–2.24)	0.3 (0.03–2.28)	
Ischemic			
n (%)	12 (0.6)	14 (0.7)	13 (0.7)
Rate per 1,000 women-years (95% CI)	1.9 (1.0–3.3)	2.2 (1.2–3.8)	2.0 (1.1–3.5)
HR (95% CI)	0.9 (0.42-2.02)	1.1 (0.52-2.35)	
Unspecified			
n (%)	3 (0.2)	2 (0.1)	2 (0.1)
Rate per 1,000 women-years (95% CI)	0.5 (0.1–1.4)	0.3 (0.0–1.2)	0.3 (0.0–1.1)
HR (95% CI)	1.5 (0.25–8.96)	1.0 (0.15–7.31)	
TIA			
n (%)	6 (0.3)	12 (0.6)	4 (0.2)
Rate per 1,000 women-years (95% CI)	0.9 (0.3–2.0)	1.9 (1.0–3.3)	0.6 (0.2–1.6)
HR (95% CI)	1.5 (0.42–5.33)	3.1 (0.99–9.52)	

CI confidence interval, *HR* hazard ratio, *TIA* transient ischemic attack

[a] Based on review by an independent adjudication board

There were four histopathologically confirmed cases of ovarian carcinoma: bazedoxifene 20 mg (n=3), bazedoxifene 40/20 mg (n=1), and placebo (n=0). For two additional subjects in the bazedoxifene 20-mg group, ovarian carcinoma was reported as an AE. Subsequent review of these histopathology reports showed a primary papillary peritoneal serous adenocarcinoma for one subject; for the other subject, the primary diagnosis was unknown. The incidence of uterine or vaginal bleeding was similar among the bazedoxifene and placebo groups.

Discussion

Overall, bazedoxifene was associated with a favorable safety and tolerability profile with no evidence of endometrial or breast stimulation over 5 years of therapy in postmenopausal women with osteoporosis; the findings at 5 years were consistent with those seen at 3 years [18]. The incidence of AEs, serious AEs, and discontinuations due to AEs in the bazedoxifene groups was similar to that observed in the placebo group. Also consistent with findings at 3 years and previous studies of SERMs [8, 10–12, 18, 21], there was a higher incidence of hot flushes and leg cramps with bazedoxifene compared with placebo at 5 years, although most of these events were mild or moderate in severity and did not lead to study discontinuation.

Treatment with bazedoxifene was associated with a higher risk of VTE compared with placebo, which was primarily due to an increased incidence of DVTs; the risk of PE or RVT was similar among the bazedoxifene and placebo groups. The majority of VTEs occurred early on, during the first 2 years of the study. Treatment with raloxifene has been associated with the highest relative risk (RR) of VTE during year 1 (RR, 6.0; 95% CI, 1.4–25.5) and year 2 (RR, 6.6; 95% CI, 0.9–50.4) [14], which decreased to 3.1 (95% CI, 0.9–10.4) during years 4 to 8 [15]. Overall, the increased risk of VTEs seen with bazedoxifene relative to placebo (HR, 1.5–1.7) over 5 years is similar to that in longer-term evaluations of raloxifene (HR, 1.4–2.1) [13, 14] and lasofoxifene (HR, 2.1–2.7) [22].

Also consistent with the 3-year findings [18], the risk of cardiac disorders (coronary occlusion, myocardial infarction, and myocardial ischemia) and stroke (ischemic, hemorrhagic, or unspecified) with bazedoxifene was similar and not significantly different from that with placebo at 5 years. Raloxifene has been associated with a small but significant increase in the incidence of fatal stroke compared with placebo over 5.6 years of follow-up (RR, 1.49; 95% CI, 1.00–2.24; P=0.05), although there has been

Table 4 Rate and hazard ratio of venous thromboembolic events and superficial thrombophlebitis over 5 years[a]

	Bazedoxifene 20 mg (n=1,886)	Bazedoxifene 40/20 mg (n=1,872)	Placebo (n=1,885)
Any VTE			
n (%)	15 (0.8)	16 (0.9)	10 (0.5)
Rate per 1,000 women-years (95% CI)	2.3 (1.3–3.9)	2.6 (1.5–4.1)	1.6 (0.8–2.9)
HR (95% CI)	1.5 (0.68–3.35)	1.7 (0.75–3.63)	
DVT			
n (%)	9 (0.5)	11 (0.6)	3 (0.2)
Rate per 1,000 women-years (95% CI)	1.4 (0.6–2.7)	1.8 (0.9–3.1)	0.5 (0.1–1.4)
HR (95% CI)	3.0 (0.81–11.09)	3.8 (1.05–13.51)	
PE			
n (%)	4 (0.2)	3 (0.2)	4 (0.2)
Rate per 1,000 women-years (95% CI)	0.6 (0.2–1.6)	0.5 (0.1–1.4)	0.6 (0.2–1.6)
HR (95% CI)	1.0 (0.25–4.01)	0.8 (0.17–3.47)	
RVT			
n (%)	2 (0.1)	2 (0.1)	3 (0.2)
Rate per 1,000 women-years (95% CI)	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)	0.7 (0.11–4.10)	
Superficial thrombophlebitis			
n (%)	13 (0.7)	21 (1.1)	10 (0.5)
Rate per 1,000 women-years (95% CI)	2.0 (1.1–3.5)	3.4 (2.1–5.1)	1.6 (0.8–2.9)
HR (95% CI)	1.3 (0.57–2.97)	2.2 (1.01–4.57)	

VTE venous thromboembolic event, *CI* confidence interval, *HR* hazard ratio, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *RVT* retinal vein thrombosis

[a] Based on review by an independent adjudication board

no evidence of a difference in the overall risk of stroke [13]. In the current study, the number of cardiovascular-related deaths (including stroke) was similar among the bazedoxifene and placebo groups. There was an increased number of TIAs observed in the bazedoxifene 40-/20-mg group compared with the other groups; this difference was not statistically significant. The similar incidence of ischemic strokes with both bazedoxifene doses relative to placebo does not support a causative relationship between bazedoxifene 40 mg and TIA.

Table 5 Incidence of breast- and reproductive system–related adverse events

Subjects, *n* (%)	Bazedoxifene 20 mg (n=1,886)	Bazedoxifene 40/20 mg (n=1,872)	Placebo (n=1,885)
Breast carcinoma	10 (0.5)[a]	9 (0.5)	10 (0.5)
Breast cyst	11 (0.6)	11 (0.6)	16 (0.8)
Fibrocystic breast disease	7 (0.4)	10 (0.5)	14 (0.7)
Breast neoplasm	16 (0.8)	18 (1.0)	22 (1.2)
Breast pain	57 (3.0)	50 (2.7)	51 (2.7)
Endometrial carcinoma*	0	3 (0.2)	6 (0.3)
Endometrial hyperplasia	1 (0.1)	1 (0.1)	1 (0.1)
Endometrial neoplasia (polyps)	13 (0.7)	16 (0.9)	14 (0.7)
Ovarian carcinoma	3 (0.2)[b]	1 (0.1)	0
Ovarian cyst	21 (1.1)	11 (0.6)	16 (0.8)
Uterine hemorrhage	4 (0.2)	6 (0.3)	5 (0.3)
Vaginal hemorrhage	19 (1.0)	22 (1.2)	28 (1.5)

*P=0.05 (chi-square test)

[a] Includes one case with breast lesion at baseline and diagnosed later on in the study

[b] Excludes 2 cases that were not confirmed as ovarian carcinoma by histopathology

Endometrial safety is an important concern with the use of SERMs due to their association with uterine stimulation. For instance, several other SERMs (e.g., idoxifene, levormeloxifene) that were under clinical evaluation for postmenopausal osteoporosis were discontinued because they were associated with adverse endometrial effects [11, 23–26].

Bazedoxifene was associated with a favorable endometrial and breast safety profile over 5 years of therapy, consistent with previous clinical investigations [16, 17, 19, 27]. There was no change in endometrial thickness in the bazedoxifene groups compared with the placebo group at 5 years. The incidence of breast- and reproductive system–related AEs with bazedoxifene was similar to that with placebo. There were fewer cases of endometrial carcinoma in the bazedoxifene groups compared with the placebo group. The number of subjects with breast cancer and fibrocystic breast disease was small and not significantly different among the bazedoxifene and placebo groups.

A reduced risk of breast cancer has been reported with tamoxifen and raloxifene [14, 28, 29]. Bazedoxifene was not associated with a decrease in breast cancer risk at 5 years, consistent with our findings at 3 years [18]. Raloxifene was also not associated with a reduction in breast cancer risk at 3 years [18], in contrast to previous reports [13, 30, 31]; this may be attributed to the relatively small number of subjects evaluated and the overall low baseline risk for breast cancer as assessed by the Gail index (5-year risk <1.6 for all groups).

Strengths of the study include the large sample size of postmenopausal women with osteoporosis who were followed for 5 years, enabling the collection of long-term safety data. There were a few potential limitations. Because only those subjects who completed the core study were eligible for enrollment in the extension, it may be possible that the extension study population was somewhat different (e.g., overall healthier) compared with the core study population. However, the baseline characteristics and demographics of subjects who continued on in the study extension were not different among groups and were generally similar to those enrolled in the core study [18]. Also, interpretation of data for subjects in the bazedoxifene 40-/20-mg group may be a challenge if considerable differences were observed between the two bazedoxifene doses; however, both the efficacy and safety findings were similar among the groups.

In conclusion, findings from this 2-year extension study showed that bazedoxifene was generally safe and well tolerated in postmenopausal women with osteoporosis, with no evidence of endometrial or breast stimulation over 5 years of therapy. The findings at 5 years were consistent with those seen at 3 years. Combined with the sustained antifracture effect seen with bazedoxifene, these findings support a favorable long-term benefit−risk profile of bazedoxifene in the treatment of osteoporosis in postmenopausal women.

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