Please note that the contents contained within this ECCEO poster (BZA 301 Safety) were previously presented at the 2007 ASBMR meeting; however, due to formatting restrictions (poster size 80 cm x 100 cm), it was not possible to include all of the data included in the poster presented at ASBMR. We have identified the following as key data for inclusion in the poster:

- **Subject demographics and baseline characteristics (Table 1)**
- **Summary of subject discontinuations (Table 2)**
- **Summary of the overall safety profile, including the incidence of all AEs, serious AEs, discontinuations due to AEs, and deaths (Table 3)**
- **Incidence of selected gynecologic and breast-related AEs (Table 4 and Figure 1)**
- **Incidence of selected AEs of special interest, including cardiovascular AEs, VTEs, hot flushes, and leg cramps (Table 5)**

In an effort to provide additional space for the data outlined above, a copy of the abstract is not included in the poster presentation.

Safety and Tolerability of Bazedoxifene in Postmenopausal Women With Osteoporosis: Results From a 3-Year, Randomized, Placebo- and Active-controlled Clinical Trial

C. E. Fernandes,[1] J. D. Adachi,[2] C. H. Chesnut,[3] J. P. Brown,[4] C. Christiansen,[5] L. A. Russo,[6] J. C. Menegoci,[7] A. Kung,[8] A. A. Chines,[9] L. Bessac[9]

[1]Women's Health and Wellness Institute (ISBEM), São Paulo, Brazil; [2]St. Joseph's Hospital, McMaster University, Hamilton, Ontario, Canada; [3]University of Washington, Seattle, WA, USA; [4]CHUL Research Center, Laval University, Quebec City, Quebec, Canada; [5]Center for Clinical and Basic Research (CCBR), Ballerup, Denmark; [6]CCBR, Rio de Janeiro, Brazil; [7]Pontifícia Universidade Católica de São Paulo, São Paulo, Brazil; [8]The University of Hong Kong, Hong Kong, China; [9]Wyeth Research, Collegeville, PA, USA.

INTRODUCTION

- Bazedoxifene (BZA) is a novel selective estrogen receptor modulator (SERM) undergoing clinical development for the prevention and treatment of postmenopausal osteoporosis
- In preclinical studies, BZA demonstrated positive estrogen agonist effects on the skeletal and cardiovascular systems with no evidence of endometrial stimulation[1,2]
  - BZA also antagonized the proliferation of MCF-7 human breast cancer cells[1,2]
- Several phase I trials have evaluated the metabolism and pharmacokinetic parameters of BZA in healthy postmenopausal women
  - Oral doses of BZA were safe and well tolerated and demonstrated linear pharmacokinetics, an improved bioavailability profile compared with other clinically available SERMs, and an elimination half-life of approximately 28 hours with minimal P450-mediated metabolism. The drug was primarily excreted in the feces (84.7%)[3-5]
- In phase II studies, doses of BZA as low as 5 mg/d produced significant reductions in markers of bone turnover compared with placebo (PBO)[6]
  - BZA doses up to 40 mg/d were well tolerated and did not stimulate the endometrium in postmenopausal women[7]
- More than 10,000 postmenopausal patients have been enrolled in 2 phase III clinical trials to evaluate BZA safety and efficacy
  - Treatment with BZA 20 and 40 mg resulted in clinically meaningful reductions in the risk of vertebral fractures (42% and 37%, respectively) compared with PBO after 36 months (refer to abstract #AB408/OC40)
  - Safety endpoints for the BZA osteoporosis treatment indication trial are summarized here

OBJECTIVE

- To evaluate the safety and tolerability of BZA in the treatment of postmenopausal osteoporosis compared with PBO and raloxifene (RLX)

METHODS

Study Design

- This was a 3-year, multicenter, double-blind, randomized, PBO- and active comparator (RLX)–controlled study (core study completed) with a 4-year double-blind study extension (ongoing)
- The study was conducted at 206 investigative sites (Asia-Pacific, Canada, Europe, Latin America, South Africa, and the United States)
- Generally healthy women (aged 55-85 years) with osteoporosis who were postmenopausal ≥2 years were enrolled
- Subjects were randomized to treatment with BZA 20 or 40 mg, RLX 60 mg, or PBO taken orally once daily for 3 years
- All subjects were supplemented daily with oral elemental calcium (up to 1,200 mg) and vitamin D (400-800 IU)

Safety

- Safety and tolerability assessments included adverse event (AE) reporting, physical and gynecologic examinations (including pelvic and breast), and clinical laboratory determinations
- All AEs included those reported at baseline up to Day 1,139 (3-year cutoff date for the core study) and included treatment-emergent AEs and post-therapy AEs
- Special attention has been paid to evaluate specific AEs of special interest, including cardiovascular AEs, venous thromboembolic AEs (VTEs), and gynecologic AEs (including endometrial and breast-related AEs)
- An endometrial safety substudy enrolled a subgroup of women who had an intact uterus
  - For subjects enrolled in the endometrial safety substudy, transvaginal ultrasonography (TVU) was performed at baseline and at Months 12 and 24 to assess endometrial thickness, ovarian volume, and the presence of ovarian cysts; endometrial biopsies were performed at baseline and at Month 24 to assess endometrial histology
- Any subjects outside of the endometrial safety substudy (ie, safety population) also underwent TVU if abnormal uterine bleeding was reported at any time during the study

Subjects

RESULTS

- A total of 7,492 subjects (mean age, 66.4 years) were randomly assigned to a treatment group, received at least 1 dose of the study drug, and were included in the safety analyses
  - Subject demographic and baseline characteristics were similar among treatment groups (**Table 1**)

Table 1. Selected Demographic and Baseline Characteristics[a]

Characteristic	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
Age, y				
Mean (SD)	66.5 (6.5)	66.2 (6.8)	66.4 (6.7)	66.5 (6.8)
Ethnic origin/race, n (%)				
White	1,657 (87.9)	1,623 (86.7)	1,618 (87.5)	1,641 (87.1)
Black	115 (6.1)	135 (7.2)	116 (6.3)	120 (6.4)
Hispanic	90 (4.8)	83 (4.4)	87 (4.7)	88 (4.7)
Other	24 (1.3)	31 (1.7)	28 (1.5)	36 (1.9)
Years since last menstrual period				
Mean (SD)	19.7 (8.6)	19.3 (8.9)	19.5 (8.7)	19.5 (8.8)
Subjects with natural menopause				
n (%)	1,706 (90.5)	1,690 (90.3)	1,700 (91.9)	1,738 (92.2)
Subjects with hot flushes				
n (%)	287 (15.2)	316 (16.9)	264 (14.3)	251 (13.3)
Hot flushes per day[b]				
Mean (SD)	2.2 (2.4)	2.1 (2.2)	1.9 (1.9)	2.0 (2.1)
BMI, kg/m²				
n	1,883	1,869	1,847	1,880
Mean (SD)	26.6 (3.8)	26.5 (3.9)	26.4 (3.8)	26.3 (3.8)

BZA, bazedoxifene; RLX, raloxifene; PBO, placebo; SD, standard deviation; BMI, body mass index.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Overall P <0.05; Chi-square analysis.

- A total of 4,991 (67%) subjects completed the 3-year study (**Table 2**)
  - Overall, the percentage of subjects who discontinued the study was similar among treatment groups

Table 2. Number (%) of Subjects Who Discontinued the 3-Year Core Study by Primary Reason[a]

Conclusion status reason, n (%)	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
Total discontinued	632 (33.5)	643 (34.3)	597 (32.3)	629 (33.4)
AE	269 (14.3)	270 (14.4)	262 (14.2)	240 (12.7)
Death	12 (0.6)	7 (0.4)	14 (0.8)	8 (0.4)
Failed to return	39 (2.1)	25 (1.3)	27 (1.5)	26 (1.4)
Subject request unrelated to study	158 (8.4)	181 (9.7)	162 (8.8)	177 (9.4)
Protocol violation	53 (2.8)	55 (2.9)	51 (2.8)	43 (2.3)
Unsatisfactory response[b,c]	52 (2.8)	52 (2.8)	39 (2.1)	75 (4.0)
Other event	49 (2.6)	53 (2.8)	42 (2.3)	60 (3.2)

BZA, bazedoxifene; RLX, raloxifene; PBO, placebo; AE, adverse event.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Unsatisfactory response was defined as the occurrence of a new vertebral fracture or a ≥7% decrease in bone mineral density of the lumbar spine or hip at any time during the study.
[c]Overall P <0.01; Chi-square analysis.

Overall Adverse Events

- A total of 7,186 (95.9%) subjects in the overall safety population reported ≥1 AE (**Table 3**)
- Overall, the incidence of AEs, serious AEs, discontinuations due to AEs, and deaths were similar among treatment groups (**Table 3**)
  - Sixty subjects died during the study period: 17 subjects in the BZA 20-mg treatment group, 13 subjects in the BZA 40-mg treatment group, 19 subjects in the RLX 60-mg treatment group, and 11 subjects in the PBO group
  - Of note, there were no deaths due to ischemic strokes
  - Eight subjects died because of myocardial ischemia or infarction (2 in each treatment group)

Table 3. Overall Summary of Safety Profile[a]

AE, n (%)	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
Any AE	1,806 (95.8)	1,792 (95.7)	1,775 (96.0)	1,813 (96.2)
Any serious AE	382 (20.3)	368 (19.7)	344 (18.6)	353 (18.7)
Discontinuations due to AE	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)

AE, adverse events; BZA, bazedoxifene; RLX, raloxifene; PBO, placebo.
[a]Incudes all subjects in the overall population; n = 7,492.

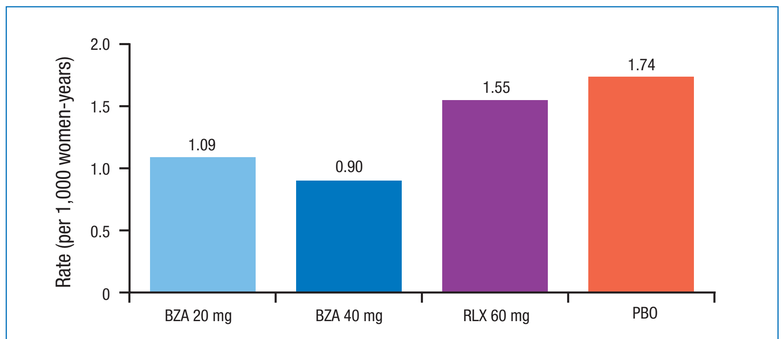
Gynecologic Safety

- BZA demonstrated a favorable gynecologic safety and tolerability profile
- No safety concerns related to the gynecologic system (including breast-related AEs) were observed in the BZA treatment groups (**Table 4**)
  - Reports of endometrial carcinoma and endometrial hyperplasia were low and similar among treatment groups
  - The number of breast cancer cases was similar among treatment groups, although the incidence was lower in the BZA treatment groups relative to the PBO or RLX 60-mg groups (**Table 4** and **Figure 1**)
    - A lower incidence of breast cyst and/or fibrocystic breast disease was observed with BZA 20 or 40 mg compared with PBO or RLX 60 mg
- TVU results were available for 753 subjects, which included 643 (85.4%) subjects enrolled in the endometrial safety substudy and 110 (14.6%) subjects in the safety population who reported abnormal uterine bleeding
  - Overall, the mean change from baseline in endometrial thickness and the number of subjects with endometrial thickness >5 mm were similar among treatment groups at baseline and at 12 and 24 months
    - Subjects in the RLX 60-mg group exhibited a significantly greater mean change from baseline in endometrial thickness compared with those in the PBO group at 12 months (P = 0.01)

Table 4. Incidence of Selected Gynecologic AEs[a]

AE, n (%)	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
Endometrial carcinoma	0	2 (0.1)	2 (0.1)	3 (0.2)
Endometrial neoplasia[b]	9 (0.5)	12 (0.6)	12 (0.6)	10 (0.5)
Endometrial hyperplasia	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Ovarian carcinoma[c]	5 (0.3)	0	2 (0.1)	0
Ovarian cyst	15 (0.8)	8 (0.4)	13 (0.7)	14 (0.7)
Uterine hemorrhage	3 (0.2)	5 (0.3)	4 (0.2)	3 (0.2)
Vaginal hemorrhage	16 (0.8)	17 (0.9)	22 (1.2)	23 (1.2)
Breast carcinoma	5 (0.3)	4 (0.2)	7 (0.4)	8 (0.4)
Breast cyst/fibrocystic breast disease[d]	13 (0.7)	12 (0.6)	31 (1.7)	18 (1.0)
Breast pain	53 (2.8)	45 (2.4)	55 (3.0)	46 (2.4)
Breast neoplasm[e]	12 (0.6)	14 (0.7)	11 (0.6)	22 (1.2)

AE, adverse event; BZA, bazedoxifene; RLX, raloxifene; PBO, placebo.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Events reported as endometrial neoplasia included endometrial polyps, uterine polyps, thickening of the endometrium due to polyps, hyperplastic endometrial polyps, accentuated cystocele and polyps, and endometrial polyps with cystic atrophy (benign).
[c]Overall P <0.05; Chi-square analysis.
[d]Overall P <0.01; Chi-square analysis.
[e]Events reported as breast neoplasm included, but were not limited to, breast mass, breast lump, lipoma, fibroadenoma, and intracanalar papilloma.



BZA, bazedoxifene; RLX, raloxifene; PBO, placebo.

Figure 1. Breast cancer incidence (36 months).

Selected Adverse Events of Special Interest

- The number of cardiovascular events was low and evenly distributed among treatment groups; there were no significant between-group differences in the incidence of strokes (**Table 5**)
- The incidence of VTEs (deep vein thrombosis and/or pulmonary embolism) was higher in the active treatment groups compared with the PBO group (**Table 5**)
  - The overall incidence of VTEs in the active treatment groups was very low (<1%)
  - There was no significant difference in the incidence of VTEs between the BZA and RLX 60-mg treatment groups
  - The higher incidence of VTEs observed in the active treatment groups was primarily the result of an increased incidence of deep vein thrombosis
- The incidence of hot flushes and leg cramps was similar among the active treatment groups and higher than that reported with PBO (**Table 5**)

Table 5. Incidence of Selected AEs of Special Interest[a]

AE, n (%)	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
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[b]	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)
Hot flushes[c]	238 (12.6)	243 (13.0)	222 (12.0)	118 (6.3)
Leg cramps[d]	205 (10.9)	204 (10.9)	216 (11.7)	155 (8.2)

AE, adverse event; BZA, bazedoxifene; RLX, raloxifene, PBO, placebo.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Overall P <0.05; Chi-square analysis.
[c]Overall P <0.001; Chi-square analysis.
[d]Overall P <0.01; Chi-square analysis.

CONCLUSIONS

- **Overall, BZA was safe and well tolerated in postmenopausal women with osteoporosis over 3 years of therapy**
- **The overall incidence of AEs, serious AEs, withdrawals due to AEs, and deaths was similar among treatment groups**
- **No safety concerns related to the cardiovascular and gynecologic systems, including the breast, were observed in the BZA treatment groups**
  - **BZA demonstrated a favorable endometrial safety profile, as evidenced by a low incidence of endometrial hyperplasia or carcinoma similar to that of PBO**
- **An increased incidence of VTEs (primarily deep vein thrombosis) was observed in the BZA and RLX 60-mg treatment groups, a finding consistent with that reported in earlier studies of SERMs[8,9]**
  - **However, the overall incidence of VTEs in the active treatment groups was very low (<1%)**
- **In this study, BZA demonstrated a favorable benefit–risk profile and thus represents a promising therapy for the treatment of postmenopausal osteoporosis**

REFERENCES

1. Komm BS, et al. *Endocrinology*. 2005;146(9):3999-4008.
2. Komm BS, Lyttle CR. *Ann N Y Acad Sci*. 2001;949:317-326.
3. Chandrasekaran A, et al. *Clin Pharmacol Ther*. 2003;73(2):P47. Abstract PII-67.
4. Ermer J, et al. *Clin Pharmacol Ther*. 2003;73(2):P46. Abstract PII-66.
5. Patat A, et al. *Clin Pharmacol Ther*. 2003;73(2):P43. Abstract PII-54.
6. Ronkin S, et al. *J Bone Miner Res*. 2001;16(suppl 1):S413. Abstract SU437.
7. Ronkin S, et al. *Obstet Gynecol*. 2005;105(6):1397-1404.
8. Ettinger B, et al. *JAMA*. 1999;282:637-645.
9. Grady D, et al. *Obstet Gynecol*. 2004;104(4):837-844.

ACKNOWLEDGMENT

This study was supported by Wyeth Research, Collegeville, PA, USA.

POSTER PRESENTED AT THE 8TH EUROPEAN CONGRESS ON CLINICAL AND ECONOMIC ASPECTS OF OSTEOPOROSIS AND OSTEOARTHRITIS, APRIL 9-12, 2008, ISTANBUL, TURKEY.

INTRODUCTION

- Bazedoxifene (BZA) is a novel selective estrogen receptor modulator (SERM) undergoing clinical development for the prevention and treatment of postmenopausal osteoporosis
- In preclinical studies, BZA demonstrated positive estrogen agonist effects on the skeletal and cardiovascular systems with no evidence of endometrial stimulation[1,2]
  - BZA also antagonized the proliferation of MCF-7 human breast cancer cells[1,2]
- Several phase I trials have evaluated the metabolism and pharmacokinetic parameters of BZA in healthy postmenopausal women
  - Oral doses of BZA were safe and well tolerated and demonstrated linear pharmacokinetics, an improved bioavailability profile compared with other clinically available SERMs, and an elimination half-life of approximately 28 hours with minimal P450-mediated metabolism. The drug was primarily excreted in the feces (84.7%)[3-5]
- In phase II studies, doses of BZA as low as 5 mg/d produced significant reductions in markers of bone turnover compared with placebo (PBO)[6]
  - BZA doses up to 40 mg/d were well tolerated and did not stimulate the endometrium in postmenopausal women[7]
- More than 10,000 postmenopausal patients have been enrolled in 2 phase III clinical trials to evaluate BZA safety and efficacy
  - Treatment with BZA 20 and 40 mg resulted in clinically meaningful reductions in the risk of vertebral fractures (42% and 37%, respectively) compared with PBO after 36 months (refer to abstract #AB408/OC40)
  - Safety endpoints for the BZA osteoporosis treatment indication trial are summarized here

OBJECTIVE

- To evaluate the safety and tolerability of BZA in the treatment of postmenopausal osteoporosis compared with PBO and raloxifene (RLX)

METHODS

Study Design

- This was a 3-year, multicenter, double-blind, randomized, PBO- and active comparator (RLX)–controlled study (core study completed) with a 4-year double-blind study extension (ongoing)
- The study was conducted at 206 investigative sites (Asia-Pacific, Canada, Europe, Latin America, South Africa, and the United States)
- Generally healthy women (aged 55-85 years) with osteoporosis who were postmenopausal ≥2 years were enrolled
- Subjects were randomized to treatment with BZA 20 or 40 mg, RLX 60 mg, or PBO taken orally once daily for 3 years
- All subjects were supplemented daily with oral elemental calcium (up to 1,200 mg) and vitamin D (400-800 IU)

Safety

- Safety and tolerability assessments included adverse event (AE) reporting, physical and gynecologic examinations (including pelvic and breast), and clinical laboratory determinations
- All AEs included those reported at baseline up to Day 1,139 (3-year cutoff date for the core study) and included treatment-emergent AEs and post-therapy AEs
- Special attention has been paid to evaluate specific AEs of special interest, including cardiovascular AEs, venous thromboembolic AEs (VTEs), and gynecologic AEs (including endometrial and breast-related AEs)
- An endometrial safety substudy enrolled a subgroup of women who had an intact uterus
  - For subjects enrolled in the endometrial safety substudy, transvaginal ultrasonography (TVU) was performed at baseline and at Months 12 and 24 to assess endometrial thickness, ovarian volume, and the presence of ovarian cysts; endometrial biopsies were performed at baseline and at Month 24 to assess endometrial histology
- Any subjects outside of the endometrial safety substudy (ie, safety population) also underwent TVU if abnormal uterine bleeding was reported at any time during the study

Subjects

RESULTS

- A total of 7,492 subjects (mean age, 66.4 years) were randomly assigned to a treatment group, received at least 1 dose of the study drug, and were included in the safety analyses
  - Subject demographic and baseline characteristics were similar among treatment groups (**Table 1**)

Table 1. Selected Demographic and Baseline Characteristics[a]

Characteristic	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
Age, y				
Mean (SD)	66.5 (6.5)	66.2 (6.8)	66.4 (6.7)	66.5 (6.8)
Ethnic origin/race, n (%)				
White	1,657 (87.9)	1,623 (86.7)	1,618 (87.5)	1,641 (87.1)
Black	115 (6.1)	135 (7.2)	116 (6.3)	120 (6.4)
Hispanic	90 (4.8)	83 (4.4)	87 (4.7)	88 (4.7)
Other	24 (1.3)	31 (1.7)	28 (1.5)	36 (1.9)
Years since last menstrual period				
Mean (SD)	19.7 (8.6)	19.3 (8.9)	19.5 (8.7)	19.5 (8.8)
Subjects with natural menopause				
n (%)	1,706 (90.5)	1,690 (90.3)	1,700 (91.9)	1,738 (92.2)
Subjects with hot flushes				
n (%)	287 (15.2)	316 (16.9)	264 (14.3)	251 (13.3)
Hot flushes per day[b]				
Mean (SD)	2.2 (2.4)	2.1 (2.2)	1.9 (1.9)	2.0 (2.1)
BMI, kg/m^2				
n	1,883	1,869	1,847	1,880
Mean (SD)	26.6 (3.8)	26.5 (3.9)	26.4 (3.8)	26.3 (3.8)

BZA, bazedoxifene; RLX, raloxifene; PBO, placebo; SD, standard deviation; BMI, body mass index.

[a]Includes all subjects in the overall population; n = 7,492.

[b]Overall $P < 0.05$; Chi-square analysis.

- A total of 4,991 (67%) subjects completed the 3-year study (**Table 2**)
  - Overall, the percentage of subjects who discontinued the study was similar among treatment groups

Table 2. Number (%) of Subjects Who Discontinued the 3-Year Core Study by Primary Reason[a]

	Treatment group			
Conclusion status reason, n (%)	**BZA 20 mg (n = 1,886)**	**BZA 40 mg (n = 1,872)**	**RLX 60 mg (n = 1,849)**	**PBO (n = 1,885)**
Total discontinued	632 (33.5)	643 (34.3)	597 (32.3)	629 (33.4)
AE	269 (14.3)	270 (14.4)	262 (14.2)	240 (12.7)
Death	12 (0.6)	7 (0.4)	14 (0.8)	8 (0.4)
Failed to return	39 (2.1)	25 (1.3)	27 (1.5)	26 (1.4)
Subject request unrelated to study	158 (8.4)	181 (9.7)	162 (8.8)	177 (9.4)
Protocol violation	53 (2.8)	55 (2.9)	51 (2.8)	43 (2.3)
Unsatisfactory response[b,c]	52 (2.8)	52 (2.8)	39 (2.1)	75 (4.0)
Other event	49 (2.6)	53 (2.8)	42 (2.3)	60 (3.2)

BZA, bazedoxifene; RLX, raloxifene; PBO, placebo; AE, adverse event.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Unsatisfactory response was defined as the occurrence of a new vertebral fracture or a ≥7% decrease in bone mineral density of the lumbar spine or hip at any time during the study.
[c]Overall $P < 0.01$; Chi-square analysis.

Overall Adverse Events

- A total of 7,186 (95.9%) subjects in the overall safety population reported ≥1 AE (**Table 3**)
- Overall, the incidence of AEs, serious AEs, discontinuations due to AEs, and deaths were similar among treatment groups (**Table 3**)
  - Sixty subjects died during the study period: 17 subjects in the BZA 20-mg treatment group, 13 subjects in the BZA 40-mg treatment group, 19 subjects in the RLX 60-mg treatment group, and 11 subjects in the PBO group
  - Of note, there were no deaths due to ischemic strokes
  - Eight subjects died because of myocardial ischemia or infarction (2 in each treatment group)

Table 3. Overall Summary of Safety Profile[a]

	Treatment group			
AE, n (%)	**BZA 20 mg (n = 1,886)**	**BZA 40 mg (n = 1,872)**	**RLX 60 mg (n = 1,849)**	**PBO (n = 1,885)**
Any AE	1,806 (95.8)	1,792 (95.7)	1,775 (96.0)	1,813 (96.2)
Any serious AE	382 (20.3)	368 (19.7)	344 (18.6)	353 (18.7)
Discontinuations due to AE	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)

AE, adverse events; BZA, bazedoxifene; RLX, raloxifene; PBO, placebo.
[a]Incudes all subjects in the overall population; n = 7,492.

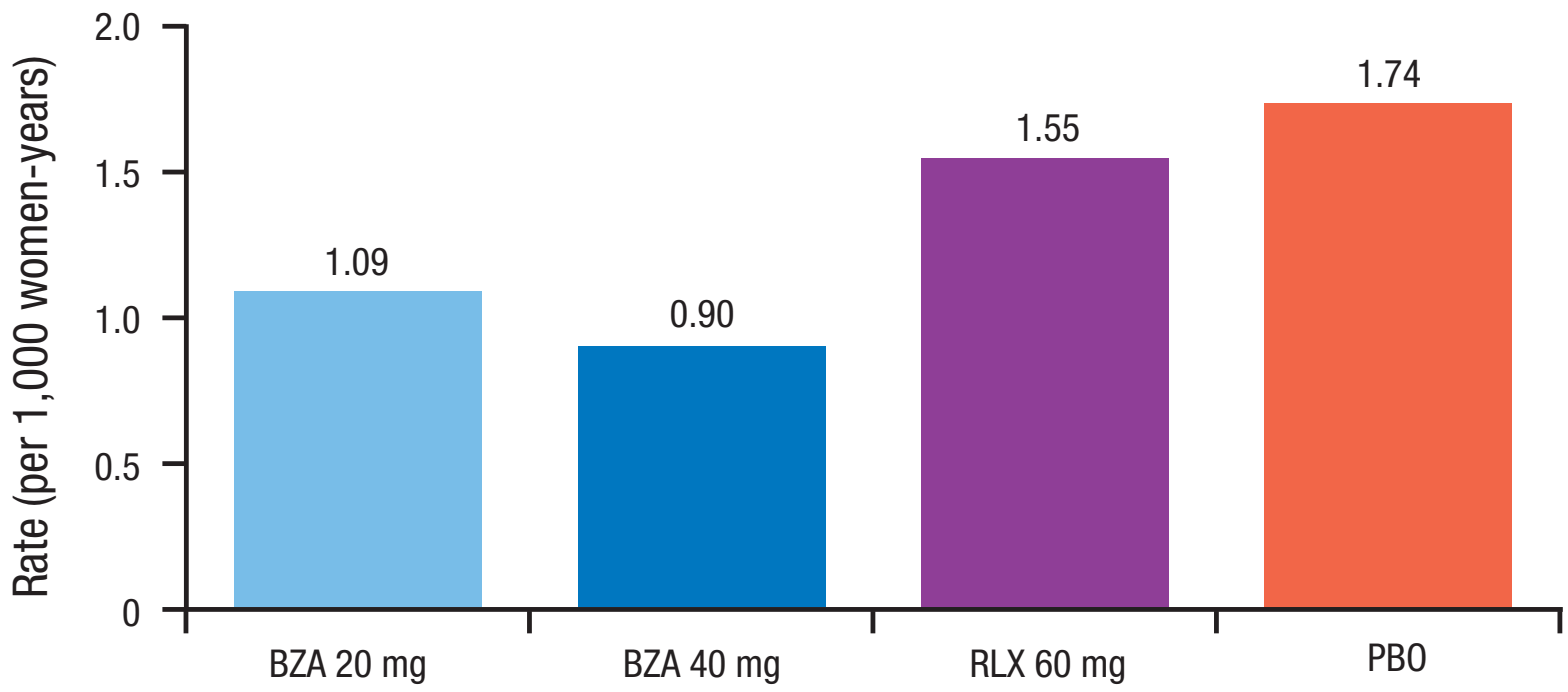
Gynecologic Safety

- BZA demonstrated a favorable gynecologic safety and tolerability profile
- No safety concerns related to the gynecologic system (including breast-related AEs) were observed in the BZA treatment groups (**Table 4**)
  - Reports of endometrial carcinoma and endometrial hyperplasia were low and similar among treatment groups
  - The number of breast cancer cases was similar among treatment groups, although the incidence was lower in the BZA treatment groups relative to the PBO or RLX 60-mg groups (**Table 4** and **Figure 1**)
    - A lower incidence of breast cyst and/or fibrocystic breast disease was observed with BZA 20 or 40 mg compared with PBO or RLX 60 mg
- TVU results were available for 753 subjects, which included 643 (85.4%) subjects enrolled in the endometrial safety substudy and 110 (14.6%) subjects in the safety population who reported abnormal uterine bleeding
  - Overall, the mean change from baseline in endometrial thickness and the number of subjects with endometrial thickness >5 mm were similar among treatment groups at baseline and at 12 and 24 months
    - Subjects in the RLX 60-mg group exhibited a significantly greater mean change from baseline in endometrial thickness compared with those in the PBO group at 12 months ($P = 0.01$)

Table 4. Incidence of Selected Gynecologic AEs[a]

	Treatment group			
AE, n (%)	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
Endometrial carcinoma	0	2 (0.1)	2 (0.1)	3 (0.2)
Endometrial neoplasia[b]	9 (0.5)	12 (0.6)	12 (0.6)	10 (0.5)
Endometrial hyperplasia	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Ovarian carcinoma[c]	5 (0.3)	0	2 (0.1)	0
Ovarian cyst	15 (0.8)	8 (0.4)	13 (0.7)	14 (0.7)
Uterine hemorrhage	3 (0.2)	5 (0.3)	4 (0.2)	3 (0.2)
Vaginal hemorrhage	16 (0.8)	17 (0.9)	22 (1.2)	23 (1.2)
Breast carcinoma	5 (0.3)	4 (0.2)	7 (0.4)	8 (0.4)
Breast cyst/fibrocystic breast disease[d]	13 (0.7)	12 (0.6)	31 (1.7)	18 (1.0)
Breast pain	53 (2.8)	45 (2.4)	55 (3.0)	46 (2.4)
Breast neoplasm[e]	12 (0.6)	14 (0.7)	11 (0.6)	22 (1.2)

AE, adverse event; BZA, bazedoxifene; RLX, raloxifene; PBO, placebo.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Events reported as endometrial neoplasia included endometrial polyps, uterine polyps, thickening of the endometrium due to polyps, hyperplastic endometrial polyps, accentuated cystocele and polyps, and endometrial polyps with cystic atrophy (benign).
[c]Overall $P < 0.05$; Chi-square analysis.
[d]Overall $P < 0.01$; Chi-square analysis.
[e]Events reported as breast neoplasm included, but were not limited to, breast mass, breast lump, lipoma, fibroadenoma, and intracanalar papilloma.



BZA, bazedoxifene; RLX, raloxifene; PBO, placebo.

Figure 1. Breast cancer incidence (36 months).

Selected Adverse Events of Special Interest

- The number of cardiovascular events was low and evenly distributed among treatment groups; there were no significant between-group differences in the incidence of strokes (**Table 5**)
- The incidence of VTEs (deep vein thrombosis and/or pulmonary embolism) was higher in the active treatment groups compared with the PBO group (**Table 5**)
  - The overall incidence of VTEs in the active treatment groups was very low (<1%)
  - There was no significant difference in the incidence of VTEs between the BZA and RLX 60-mg treatment groups
  - The higher incidence of VTEs observed in the active treatment groups was primarily the result of an increased incidence of deep vein thrombosis
- The incidence of hot flushes and leg cramps was similar among the active treatment groups and higher than that reported with PBO (**Table 5**)

Table 5. Incidence of Selected AEs of Special Interest[a]

	Treatment group			
AE, n (%)	BZA 20 mg (n = 1,886)	BZA 40 mg (n = 1,872)	RLX 60 mg (n = 1,849)	PBO (n = 1,885)
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[b]	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)
Hot flushes[c]	238 (12.6)	243 (13.0)	222 (12.0)	118 (6.3)
Leg cramps[d]	205 (10.9)	204 (10.9)	216 (11.7)	155 (8.2)

AE, adverse event; BZA, bazedoxifene; RLX, raloxifene, PBO, placebo.
[a]Includes all subjects in the overall population; n = 7,492.
[b]Overall $P < 0.05$; Chi-square analysis.
[c]Overall $P < 0.001$; Chi-square analysis.
[d]Overall $P < 0.01$; Chi-square analysis.

CONCLUSIONS

- **Overall, BZA was safe and well tolerated in postmenopausal women with osteoporosis over 3 years of therapy**
- **The overall incidence of AEs, serious AEs, withdrawals due to AEs, and deaths was similar among treatment groups**
- **No safety concerns related to the cardiovascular and gynecologic systems, including the breast, were observed in the BZA treatment groups**
  - **BZA demonstrated a favorable endometrial safety profile, as evidenced by a low incidence of endometrial hyperplasia or carcinoma similar to that of PBO**
- **An increased incidence of VTEs (primarily deep vein thrombosis) was observed in the BZA and RLX 60-mg treatment groups, a finding consistent with that reported in earlier studies of SERMs[8,9]**
  - **However, the overall incidence of VTEs in the active treatment groups was very low (<1%)**
- **In this study, BZA demonstrated a favorable benefit–risk profile and thus represents a promising therapy for the treatment of postmenopausal osteoporosis**

REFERENCES

1. Komm BS, et al. *Endocrinology*. 2005;146(9):3999-4008.
2. Komm BS, Lyttle CR. *Ann N Y Acad Sci*. 2001;949:317-326.
3. Chandrasekaran A, et al. *Clin Pharmacol Ther*. 2003;73(2):P47. Abstract PII-67.
4. Ermer J, et al. *Clin Pharmacol Ther*. 2003;73(2):P46. Abstract PII-66.
5. Patat A, et al. *Clin Pharmacol Ther*. 2003;73(2):P43. Abstract PII-54.
6. Ronkin S, et al. *J Bone Miner Res*. 2001;16(suppl 1):S413. Abstract SU437.
7. Ronkin S, et al. *Obstet Gynecol*. 2005;105(6):1397-1404.
8. Ettinger B, et al. *JAMA*. 1999;282:637-645.
9. Grady D, et al. *Obstet Gynecol*. 2004;104(4):837-844.

ACKNOWLEDGMENT

This study was supported by Wyeth Research, Collegeville, PA, USA.

Safety and Tolerability of Bazedoxifene in Postmenopausal Women With Osteoporosis: Results From a 3-Year, Randomized, Placebo- and Active-controlled Clinical Trial

C. E. Fernandes,[1] J. D. Adachi,[2] C. H. Chesnut,[3] J. P. Brown,[4] C. Christiansen,[5] L. A. Russo,[6] J. C. Menegoci,[7] A. Kung,[8] A. A. Chines,[9] L. Bessac[9]

[1]Women's Health and Wellness Institute (ISBEM), São Paulo, Brazil; [2]St. Joseph's Hospital, McMaster University, Hamilton, Ontario, Canada; [3]University of Washington, Seattle, WA, USA; [4]CHUL Research Center, Laval University, Quebec City, Quebec, Canada; [5]Center for Clinical and Basic Research (CCBR), Ballerup, Denmark; [6]CCBR, Rio de Janeiro, Brazil; [7]Pontifícia Universidade Católica de São Paulo, São Paulo, Brazil; [8]The University of Hong Kong, Hong Kong, China; [9]Wyeth Research, Collegeville, PA, USA.

POSTER PRESENTED AT THE 8TH EUROPEAN CONGRESS ON CLINICAL AND ECONOMIC ASPECTS OF OSTEOPOROSIS AND OSTEOARTHRITIS, APRIL 9-12, 2008, ISTANBUL, TURKEY.