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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Duavee® / Duavive® / Conjugated Estrogens 0.45 mg / Bazedoxifene 20 mg

PROTOCOL NO.: 3115A1-3307-WW (B2311009)

PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-and Active-Controlled Efficacy and Safety Study of the Effects of Bazedoxifene/Conjugated Estrogens Combinations on Endometrial Hyperplasia and Prevention of Osteoporosis in Postmenopausal Women

Study Centers: One hundred sixty six (166) centers took part in the study and randomized subjects; 131 in the United States (US), 8 in Hungary, 5 in Poland, 4 in Argentina, 3 each in Australia, Denmark, New Zealand and Columbia, 2 each in Norway and Finland, 1 each in Mexico and Chile.

Study Initiation and Final Completion Dates: 26 January 2009 to 08 February 2011

Phase of Development: Phase 3

Study Objectives:

Primary:

Safety: To confirm the endometrial safety of bazedoxifene (BZA) 20 mg/conjugated estrogens (CE) 0.45 mg and BZA 20 mg/CE 0.625 mg based on an endometrial hyperplasia incidence of <1% at Year 1.

Efficacy: To assess the effect of BZA/CE in preventing postmenopausal osteoporosis at Year 1 (osteoporosis substudy [OSS]).

Secondary:

- To assess the effect of BZA/CE compared to BZA 20 mg on the change in bone mineral density (BMD) (OSS).
- To assess the effect of BZA/CE versus (vs) placebo and CE/medroxyprogesterone acetate (MPA) on uterine bleeding/spotting.
- To assess the effect of BZA/CE vs placebo and CE/MPA on breast tenderness.

- To demonstrate non-inferiority of BZA/CE to placebo on quantitative changes in mammographic breast density in postmenopausal women at Year 1 (breast density substudy).

- To assess the effect of BZA/CE vs placebo and BZA 20 mg on bone turnover markers (BTM; OSS).

- To assess the effect of BZA/CE vs placebo on sleep parameters in a subset of women (sleep substudy) with bothersome vasomotor symptoms (VMS) at Baseline.

- To provide a descriptive comparison of BZA/CE to CE/MPA.

METHODS

Study Design: This was a Phase 3, outpatient, multicenter, double-blind, randomized, placebo- and active-controlled study in generally healthy, postmenopausal, female subjects with menopausal symptoms. This study included a main study in addition to 3 substudies (ie, a breast density substudy, an OSS, and a sleep substudy).

All subjects participated in the main study and were randomized and stratified by whether they were in the OSS or not. The randomization ratio for the main study and the OSS was 2:2:1:1:2, ie, 2 for each BZA/CE dose (BZA 20 mg/CE 0.45 mg, and BZA 20 mg/CE 0.625 mg), 1 for BZA 20 mg, 1 for CE 0.45 mg/MPA 1.5 mg, and 2 for placebo. Subjects could participate in the sleep and breast density substudies based on the respective entry criterion. A subject could participate in more than one substudy.

Subjects participated in the study for approximately 14.5 months. This included a 2-month screening period (Visit 1B at Weeks -8 to -1), a 12-month double-blind treatment period (Visits 2, 3, 4, 5, and 6 at Weeks 0, 13, 26, 39, and 52, respectively), and a 2-week follow-up phone call (Week 54). Some subjects required a washout period before entry into the study, which occurred within the 12 weeks before screening (Visit 1A at Weeks -20 to -8).

A flowchart of the basic study assessments is presented in Table 1.

Table 1. Study Flowchart

Visit Number	1A[a]	1B	2	3	4	5	6	Follow-Up
Relative Week	**20 to -8**	**-8 to -1**	**0**	**13**	**26**	**39**	**52**	**54**
Interval Flexibility				**13 to 14**	**25 to 27**	**38 to 40**	**50 to 52**	**54**
Study Interval	**Screening**		**Active Phase**					**Follow-Up**
Informed consent[b]	X							
Medical history[c]		X						
Physical examination[d]		X			X		X	
Vital signs[e]		X	X		X		X	
ECG[f]		X					X	
Laboratory screen[g]		X		X	X		X	
Pelvic examination		X					X	
Pap smear		X					X	
Transvaginal ultrasound		X					X[h]	
Endometrial biopsy		X					X[h]	
Bone turnover markers[i]		X		X	X		X	
Mammography[j]		X					X	
BMD[k]		2X			X		2X	
Questionnaires (MENQOL, MOS sleep scale)[l]			X	X			X	
Diary[m]	X----------							----------X
Randomization[n]			X					
Dispense test article			X	X	X	X		
Collect test article				X	X	X	X	
Prior/concomitant medications	X----------							----------X
Adverse events	X----------							----------X

BI-RADS = breast imaging reporting and data system; BMD = bone mineral density; ECG = electrocardiogram; LNMP = last natural menstrual period; MENQOL = menopause-specific quality of life; MOS = medical outcomes study; OSS = osteoporosis substudy; TVU = transvaginal ultrasound.

a. A washout period for subjects on hormonal therapies was required before Visit 1B. For subjects who did not require a washout, Visits 1A and 1B may have been combined.
b. An institutional review board/independent ethics committee approved written informed consent form must have been signed and dated before any screening procedures, including washout, were performed.
c. Medical history included collection of information for the breast cancer risk assessment and the fracture risk assessment at Visit 1B.
d. Physical examinations at Visits 1B, and 6 or at early withdrawal included complete physical examination and breast examination. Physical examination at Visit 4 included physical examination only.
e. Vital signs included sitting blood pressure at Visits 1B, 2, 4, and 6 or at early withdrawal and weight (kg) at Visit 1B, 4 and 6 or early withdrawal. Height (cm) was measured only at Visit 1B.
f. A 12-lead ECG was performed at Visits 1B and 6 or at early withdrawal.
g. Laboratory determinations including hematology, blood chemistry, and urinalysis were performed at Visits 1B, 3, 4 and 6 or at early withdrawal. The urinalysis was performed before the pap smear and endometrial biopsy. A sex hormone-binding globulin was performed at Visits 1B, 4 and 6. In addition, follicle-stimulating hormone (for subjects with uncertain LNMP or subjects with >6 months but <12 months since LNMP) was performed at Visit 1B. For the OSS, intact parathyroid hormone and 25-hydroxy-vitamin D levels were performed at Visit 1B, coagulation studies were performed at Visits 1B, 4 and 6.
h. The TVU was performed before the endometrial biopsy. If the TVU at Visit 6 or at early withdrawal occurring after 13 weeks identified double-walled endometrial thickness >8 mm or focal endometrial abnormality, the subject was to have a hysteroscopy with directed biopsy instead of a routine endometrial biopsy.
i. For the OSS, bone turnover markers was performed Visits 1B, 3, 4 and 6.
j. For subjects who were not in the breast density substudy, a previous mammogram within 3 months of randomization was acceptable provided that copies of the radiographs and reports were obtained. (To be enrolled in the study, subjects were required to have a screening mammography result of BI-RADS 1 or 2). Mammograms were performed at Visits 1B and 6 or at early withdrawal occurring after 26 weeks. For the breast density substudy, subject must have had a digital mammogram.
k. For the OSS, BMD measurement was performed by dual-energy x-ray absorptiometry at Visits 1B, 4 and 6, or early withdrawal occurring after 26 weeks during the first year.

Table 1. Study Flowchart

l. The MENQOL and the MOS sleep scale were obtained at Visits 2, 3 and 6 for all subjects.
m. Diaries were dispensed at Visits 1A, 1B, 2, 3, 4, 5, and 6 for subjects requiring washout and captured concomitant medication taken and symptoms/complaints. In addition, diaries dispensed at Visits 1B, 2, 3, 4, and 5 were to capture uterine bleeding/spotting and breast tenderness.
n. Randomization followed confirmation that all inclusion and no exclusion criteria were met. Subjects were instructed to begin taking test article the next day after randomization.

Number of Subjects (Planned and Analyzed): Approximately 1720 subjects were planned to participate in the main study and 1886 subjects were randomly assigned to treatment, of which 1843 subjects were treated (445 to BZA 20 mg/CE 0.45 mg, 474 to BZA 20 mg/CE 0.625 mg, 230 to BZA 20 mg, 220 to CE 0.45/MPA 1.5 mg and 474 to placebo). The randomized subjects included 1474 in the US, 40 in Hungary, 11 each in Norway, Australia and New Zealand, 63 in Finland, 159 in Denmark, 31 each in Poland and Argentina, 36 in Columbia, 4 in Mexico, 15 in Chile.

A total of 602 subjects participated in the OSS and 590 received test article (135 received BZA 20 mg/CE 0.45 mg, 154 received BZA 20 mg/CE 0.625 mg, 73 received BZA 20 mg, 70 received CE 0.45 mg/MPA 1.5 mg and 158 received placebo).

A total of 472 subjects participated in the sleep substudy and 459 received test article (115 received BZA 20 mg/CE 0.45 mg, 123 received BZA 20 mg/CE 0.625 mg, 49 received BZA 20 mg, 56 received CE 0.45 mg/MPA 1.5 mg and 116 received placebo).

A total of 961 subjects participated in the breast density substudy and 940 received test article (231 received BZA 20 mg/CE 0.45 mg, 247 received BZA 20 mg/CE 0.625 mg, 122 received BZA 20 mg, 100 received CE 0.45 mg/MPA 1.5 mg and 240 received placebo).

Diagnosis and Main Criteria for Inclusion: The study included generally healthy, postmenopausal women with an intact uterus, aged 40 to 64 years with at least 12 months of spontaneous amenorrhea, or 6 months spontaneous amenorrhea with follicle-stimulating hormone levels >40 mIU/mL.

To be eligible for the OSS, the subject's last natural menstrual cycle should not have been <5 years before Screening, and subjects were required to have at Screening, 2 evaluable BMD scans of the spine and total hip that differed by <5% and <7.5%, respectively.

To be eligible for the sleep substudy, subjects must have responded "Yes" to the following questions: "are you very bothered by hot flushes or night sweats, do you often awake during sleep time and have trouble falling asleep again, and do you feel that you often do not get the amount of sleep needed during sleep time?".

To be eligible for the breast density substudy, subjects had to have a digital mammogram that was technically acceptable for reading at Screening.

Subjects with following criteria were excluded: use of oral estrogen, progestin, androgen, or selective estrogen receptor modulator containing drug products within 8 weeks before Screening; history or active presence of clinically important medical disease:

eg, cardiovascular disease (stroke, heart attack), chronic renal or liver disease, breast cancer, etc.

Study Treatment: Test article and active comparators were provided as single tablets, over-encapsulated for blinding to matching placebo capsules. Subjects were administered 1 capsule orally, with or without food, once daily, at approximately the same time each day continuously throughout the duration of the treatment period. Subjects were randomly assigned to receive 1 of the treatment regimens presented in Table 2 for the 12-month double-blind treatment period.

Table 2. Treatment Regimens

Regimen	Capsule
1	BZA 20 mg/CE 0.45 mg
2	BZA 20 mg/CE 0.625 mg
3	BZA 20 mg
4	CE 0.45 mg/MPA 1.5 mg
5	Placebo

BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate.

Efficacy Endpoints: Efficacy was assessed by endometrial biopsies, BMD (measured by dual-energy x-ray absorptiometry), BTMs, digital mammograms, the use of daily diary cards for uterine bleeding/spotting and breast tenderness, the menopause-specific quality of life (MENQOL) questionnaire and the Medical Outcomes Study (MOS) Sleep Scale.

Primary Endpoints:

- Incidence of endometrial hyperplasia at Year 1.
- For the OSS, percent change from Baseline in BMD of the lumbar spine at Year 1.

Secondary Endpoints:

- For the OSS, percent change from Baseline in BMD of the lumbar spine and hip at Month 6 and change from Baseline in BMD of the hip at Year 1.
- For the OSS, change in BTMs at Month 6 and Year 1.
- Proportion of subjects with cumulative amenorrhea from Day 1 to Day 364.
- For the breast density substudy, the percent change in breast density at Year 1.
- For the sleep substudy, change from Baseline in sleep parameters assessed using the MOS Sleep Scale in a subset of women (sleep substudy) with bothersome VMS at Week 13.

Safety Evaluations: Safety was evaluated using the following safety assessments: scheduled physical examinations (including breast examinations), pelvic examinations, vital signs (including blood pressure and weight), endometrial biopsies, Papanicolaou (pap)

smears, clinical laboratory evaluations, transvaginal ultrasounds (TVUs), electrocardiograms (ECGs), and mammograms, and assessing adverse events (AEs).

Statistical Methods: The primary analysis population for endometrial hyperplasia was the efficacy evaluable (EE) population, which was defined as subjects who were randomly assigned and took ≥1 dose of the test article, who had a screening endometrial biopsy with readings by at least 2 blinded central pathologists, had a biopsy during Month 12, or had hyperplasia diagnosed before Month 12 and had no major protocol violations.

Endometrial hyperplasia data were also analyzed based on a modified intent-to-treat (MITT) population, which included all randomized subjects who took ≥1 dose of test article and had Baseline biopsy data and on-therapy biopsy data.

For the OSS, the primary analysis of BMD and BTM data was based on the MITT population that included all randomized subjects who were enrolled in the OSS, took ≥1 dose of test article, and had a Baseline value and ≥1 post-baseline value for the given endpoint.

The MITT population was used to analyze bleeding endpoints, and included all subjects randomized into in the study who took ≥1 dose of test article and had ≥1 day of on-therapy bleeding data.

The primary analysis of breast pain data was based on the MITT population, which included all subjects randomized into the study who took ≥1 dose of test article and had ≥20 days of data available at Screening and ≥20 continuous days of data in at least one 4-week interval after Baseline.

For the sleep substudy, the primary analysis of MENQOL and MOS sleep scale was based on MITT population, which included all randomized subjects who met the inclusion criteria for the sleep substudy and had a Baseline evaluation and ≥1 post-baseline evaluation for the respective endpoint.

For the breast density substudy, to test the non-inferiority over the placebo group, the primary analysis of breast density data was based on the per protocol (PP) population, which included all subjects who enrolled in the breast density substudy, who had a Baseline breast density evaluation and ≥1 post-baseline evaluation and did not have substantial protocol violations.

Additionally, there were analyses based on the MITT population that included all randomized subjects who took ≥1 dose of test article and had a Baseline evaluation and ≥1 post-baseline evaluation.

The safety population included all randomized subjects who took ≥1 dose of test article. The analysis of disposition, AEs, concomitant medication, and compliance was based on the safety population.

The incidence of endometrial hyperplasia or malignancy at Month 12 for each treatment group was calculated for the EE population (the primary analysis population for endometrial

hyperplasia) as: I = A/B, where I = incidence at Month 12 evaluation; A = all subjects in the EE population with biopsy results positive for endometrial hyperplasia or malignancy during the first 12 months; B = all subjects in the EE population. For all treatment groups, the incidence of endometrial malignancy at 12 months and the associated exact 1-sided and 2-sided 95% confidence interval (CI) were calculated.

For BMD and BTM the percentage change from Baseline was analyzed by analysis of covariance (ANCOVA), with treatment and region as main effects and Baseline BMD and years since menopause as covariates. The comparisons between the BZA/CE groups and placebo were the primary comparisons. In addition, the BZA 20 mg and CE/MPA groups were compared with placebo. All pairwise comparisons were based on the Wald test (based on adjusted means and pooled error term obtained from the ANCOVA). These comparisons were 2-sided at the 0.05 level. Each BZA/CE group found to be significantly better than placebo was then compared with BZA 20 mg. The comparison with BZA 20 mg was initially done as a non-inferiority test, with a non-inferiority margin of 0.5%. The difference between groups was calculated as BZA - BZA/CE. If the upper limit of the 2-sided 95% CI on this difference was <0.5, then the pertinent BZA/CE treatment was declared non-inferior. If non-inferiority was shown, the CI was evaluated for superiority (ie, the upper limit of the 2 sided 95% CI was <0). A responder was defined as a subject who had no change or had an increase from the Baseline in observed BMD data at Year 1 (Last Observation Carried Forward [LOCF] and Observed Cases) separately for lumbar spine and total hip parameters. Subjects with bone loss were defined as those who had specific percentage decreases in lumbar spine and total hip BMD from Baseline to Year 1, with the degree of bone loss ranging from >1% through >7%. Fisher's Exact test was used for the pairwise comparisons for responder and bone loss analyses.

The change from Baseline in breast density was analyzed using ANCOVA with treatment and region as factors and Baseline as the covariate. A 95% 2-sided CI on the adjusted mean differences between each BZA/CE treatment group and the placebo group were calculated as (BZA/CE-placebo). Non-inferiority of BZA/CE compared with placebo was established if the upper limit of the 2-sided 95% CI on these differences was <1.5%. The percentage of days with breast pain was compared among treatment groups using ANCOVA with treatment and region as factors and Baseline percentage of days with breast pain as the covariate. The pairwise comparisons were the BZA/CE treatment groups vs the placebo and the CE/MPA group, and were done using the t-test (based on adjusted means and the pooled error term obtained from the ANCOVA).

For the MOSs that used the MOS Sleep Scale and MENQOL assessment tools, the change from Baseline was analyzed using ANCOVA with treatment group and region as factors, and Baseline score as covariate. The pairwise comparisons were the BZA/CE treatment groups vs the placebo, CE/MPA group, and the BZA 20 mg group and were done using the Wald test (based on adjusted means and the pooled error term obtained from the ANCOVA).

RESULTS

Subject Disposition and Demography: A total of 4774 subjects were screened; 2888 were screen failures and 1886 subjects were randomized in the main study. The subject disposition is summarized by population subsets in Table 3.

Table 3. Summary of Subject Status: Number (%) of Subjects by Population Subset

Population Subset	BZA 20 mg/ CE 0.45 mg	BZA 20 mg/ CE 0.625 mg	BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo	Total
Test article not used	10 (2.2)	7 (1.5)	9 (3.8)	8 (3.5)	9 (1.9)	43 (2.3)
Safety[a]	445 (97.8)	474 (98.5)	230 (96.2)	220 (96.5)	474 (98.1)	1843 (97.7)
Main study						
Randomly assigned	455	481	239	228	483	1886
EE population[b]						
Included	335 (75)	368 (78)	169 (73)	149 (68)	354 (75)	1375 (75)
Excluded[c]	110 (25)	106 (22)	61 (27)	71 (32)	120 (25)	468 (25)
MITT population						
Included	357 (80)	388 (82)	177 (77)	169 (77)	374 (79)	1465 (79)
Excluded[c]	88 (20)	86 (18)	53 (23)	51 (23)	100 (21)	378 (21)
Osteoporosis substudy[d]						
Randomly assigned and dosed	135	154	73	70	158	590
MITT[c] population						
Included	119 (88)	139 (90)	56 (77)	59 (84)	139 (88)	512 (87)
Excluded[c]	16 (12)	15 (10)	17 (23)	11 (16)	19 (12)	78 (13)
PP population[e]						
Month 12						
Included	108 (80)	123 (80)	54 (74)	50 (71)	125 (79)	460 (78)
Excluded[c]	27 (20)	31 (20)	19 (26)	20 (29)	33 (21)	130 (22)
Breast density substudy						
Randomly assigned and dosed	231	247	122	100	240	940
PP population						
Included	189 (82)	197 (80)	98 (80)	70 (70)	188 (78)	742 (79)
Excluded[c]	42 (18)	50 (20)	24 (20)	30 (30)	52 (22)	198 (21)
MITT population						
Included	189 (82)	198 (80)	99 (81)	70 (70)	191 (80)	747 (79)
Excluded[c]	42 (18)	49 (20)	23 (19)	30 (30)	49 (20)	193 (21)
Sleep substudy						
Randomly assigned and dosed	115	123	49	56	116	459
MITT population						
Included	112 (97)	122 (99)	48 (98)	52 (93)	111 (96)	445 (97)
Excluded[c]	3 (3)	1 (<1)	1 (2)	4 (7)	5 (4)	14 (3)

BZA = bazedoxifene; CE = conjugated estrogens; EE = efficacy evaluable; MITT = modified intent-to-treat; MPA = medroxyprogesterone acetate; PP = per-protocol.

a. Safety population included all randomly assigned subjects who took at least 1 dose of test article.
b. Populations were the same for Definition 1 and Definition 2. For Definition 1, the outcome was determined to be hyperplasia when the 3 pathologists disagreed but at least 1 pathologist determined hyperplasia. Definition 2 required that a diagnosis of hyperplasia was made if at least 2 of the 3 pathologists agreed on the diagnosis.
c. A subject may have been excluded for >1 reason.
d. Osteoporosis substudy subjects.
e. Lumbar spine.

The number of subjects who completed or discontinued the study are presented in Table 4.

Table 4. Number (%) of Subjects Who Completed or Discontinued Study (by Primary Reason for Withdrawal)

Conclusion Status Reason[a]	Overall p-Value[b]	BZA 20 mg/ CE 045 mg	BZA 20 mg/ CE 0.625 mg	BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo	Total
Total		445 (100)	474 (100)	230 (100)	220 (100)	474 (100)	1843 (100)
Completed	0.027	357 (80.2)	393 (82.9)	185 (80.4)	159 (72.3)	383 (80.8)	1477 (80.1)
Discontinued	0.027	88 (19.8)	81 (17.1)	45 (19.6)	61 (27.7)	91 (19.2)	366 (19.9)
Adverse event	0.012	34 (7.6)	33 (7.0)	16 (7.0)	31 (14.1)	33 (7.0)	147 (8.0)
Death	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Investigator request	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Lost to follow-up	0.092	8 (1.8)	10 (2.1)	11 (4.8)	8 (3.6)	9 (1.9)	46 (2.5)
Other	0.043	6 (1.3)	4 (0.8)	6 (2.6)	2 (0.9)	15 (3.2)	33 (1.8)
Protocol violation	0.110	8 (1.8)	9 (1.9)	4 (1.7)	9 (4.1)	5 (1.1)	35 (1.9)
Subject request	0.016	27 (6.1)	18 (3.8)	2 (0.9)	7 (3.2)	16 (3.4)	70 (3.8)
Unsatisfactory response (efficacy)[c]	0.376	5 (1.1)	6 (1.3)	6 (2.6)	4 (1.8)	12 (2.5)	33 (1.8)

BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.
c. Reasons were unspecified.

The subjects who completed or who were withdrawn from the OSS are presented in Table 5.

Table 5. Number (%) of Subjects Who Completed or Who Were Withdrawn From the Study, by Primary Reason for Withdrawal (Osteoporosis Substudy Subjects)

Conclusion Status Reason[a]	Overall p-Value[b]	BZA 20 mg/ CE 045 mg	BZA 20 mg/ CE 0.625 mg	BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo	Total
Total		135 (100)	154 (100)	73 (100)	70 (100)	158 (100)	590 (100)
Completed	0.197	109 (80.7)	131 (85.1)	55 (75.3)	51 (72.9)	129 (81.6)	475 (80.5)
Discontinued	0.197	26 (19.3)	23 (14.9)	18 (24.7)	19 (27.1)	29 (18.4)	115 (19.5)
Adverse event	0.490	10 (7.4)	9 (5.8)	7 (9.6)	8 (11.4)	9 (5.7)	43 (7.3)
Investigator request	0.586	0	1 (0.6)	0	0	0	1 (0.2)
Lost to follow-up	0.064	1 (0.7)	3 (1.9)	3 (4.1)	3 (4.3)	0	10 (1.7)
Other	0.096	3 (2.2)	0	2 (2.7)	0	6 (3.8)	11 (1.9)
Protocol violation	0.450	2 (1.5)	3 (1.9)	2 (2.7)	4 (5.7)	4 (2.5)	15 (2.5)
Subject request	0.218	9 (6.7)	6 (3.9)	0	2 (2.9)	7 (4.4)	24 (4.1)
Unsatisfactory response (efficacy)	0.101	1 (0.7)	1 (0.6)	4 (5.5)	2 (2.9)	3 (1.9)	11 (1.9)

BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.

The subjects who completed or who were withdrawn from the breast density substudy are presented in Table 6.

Table 6. Number (%) of Subjects Who Completed or Who Were Withdrawn From the Study, by Primary Reason for Withdrawal (Breast Density Substudy Subjects)

Conclusion Status Reason[a]	Overall p-Value[b]	Treatment					
		BZA 20 mg/ CE 0.45 mg n=231	BZA 20 mg/ CE 0.625 mg n=247	BZA 20 mg n=122	CE 0.45 mg/ MPA 1.5 mg n=100	Placebo n=240	Total n=940
Total		231 (100)	247 (100)	122 (100)	100 (100)	240 (100)	940 (100)
Completed	0.594	192 (83.1)	205 (83.0)	100 (82.0)	76 (76.0)	197 (82.1)	770 (81.9)
Discontinued	0.594	39 (16.9)	42 (17.0)	22 (18.0)	24 (24.0)	43 (17.9)	170 (18.1)
Adverse event	0.180	17 (7.4)	17 (6.9)	8 (6.6)	13 (13.0)	13 (5.4)	68 (7.2)
Investigator request	0.590	0	1 (0.4)	0	0	0	1 (0.1)
Lost to follow-up	0.337	2 (0.9)	5 (2.0)	5 (4.1)	2 (2.0)	4 (1.7)	18 (1.9)
Other	0.218	3 (1.3)	1 (0.4)	2 (1.6)	0	6 (2.5)	12 (1.3)
Protocol violation	0.175	3 (1.3)	7 (2.8)	2 (1.6)	5 (5.0)	3 (1.3)	20 (2.1)
Subject request	0.342	12 (5.2)	7 (2.8)	2 (1.6)	2 (2.0)	10 (4.2)	33 (3.5)
Unsatisfactory response (efficacy)	0.567	2 (0.9)	4 (1.6)	3 (2.5)	2 (2.0)	7 (2.9)	18 (1.9)

BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; n = number of subjects in a treatment group.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.

The subjects who completed or who were withdrawn from the sleep substudy are presented in Table 7.

Table 7. Number (%) of Subjects Who Completed or Who Were Withdrawn From the Study, by Primary Reason for Withdrawal (Sleep Substudy Subjects)

Conclusion Status Reason[a]	Overall p-Value[b]	Treatment					
		BZA 20 mg/ CE 0.45 mg n=115	BZA 20 mg/ CE 0.625 mg n=123	BZA 20 mg n=49	CE 0.45 mg/ MPA 1.5 mg n=56	Placebo n=116	Total n=459
Total		115 (100)	123 (100)	49 (100)	56 (100)	116 (100)	459 (100)
Completed	0.117	93 (80.9)	102 (82.9)	40 (81.6)	37 (66.1)	93 (80.2)	365 (79.5)
Discontinued	0.117	22 (19.1)	21 (17.1)	9 (18.4)	19 (33.9)	23 (19.8)	94 (20.5)
Adverse event	0.061	9 (7.8)	6 (4.9)	3 (6.1)	10 (17.9)	10 (8.6)	38 (8.3)
Investigator request	0.603	0	1 (0.8)	0	0	0	1 (0.2)
Lost to follow-up	0.081	2 (1.7)	2 (1.6)	2 (4.1)	5 (8.9)	3 (2.6)	14 (3.1)
Other	0.278	2 (1.7)	0	0	1 (1.8)	0	3 (0.7)
Protocol violation	0.927	2 (1.7)	1 (0.8)	1 (2.0)	1 (1.8)	1 (0.9)	6 (1.3)
Subject request	0.346	7 (6.1)	7 (5.7)	0	1 (1.8)	5 (4.3)	20 (4.4)
Unsatisfactory response (efficacy)	0.190	0	4 (3.3)	3 (6.1)	1 (1.8)	4 (3.4)	12 (2.6)

BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; n = number of subjects in a treatment group.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.

Selected demographic and Baseline characteristics for the 1843 subjects in the safety population, for the 590 subjects in the OSS, for the 940 subjects in the breast density substudy, and for the 459 subjects in the sleep substudy are summarized by treatment group in Table 8, Table 9, Table 10, and Table 11 respectively.

Table 8. Selected Demographic and Other Baseline Characteristics Summary (Safety Population)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=445)	BZA 20 mg/ CE 0.625 mg (n=474)	BZA 20 mg (n=230)	CE 0.45 mg/ MPA 1.5 mg (n=220)	Placebo (n=474)	Total (n=1843)
Age (years)							
N		445	474	230	220	474	1843
Mean	0.396[a]	54.43	53.89	54.07	54.15	54.19	54.15
Standard deviation		4.02	4.00	4.01	4.50	4.07	4.09
Minimum - maximum		43.00-64.00	43.00-64.00	42.00-64.00	42.00-64.00	41.00-64.00	41.00-64.00
Ethnic origin	0.340[b]						
Hispanic or Latino		50 (11.24)	56 (11.81)	32 (13.91)	24 (10.91)	42 (8.86)	204 (11.07)
Non-Hispanic and Non-Latino		395 (88.76)	418 (88.19)	198 (86.09)	196 (89.09)	432 (91.14)	1639 (88.93)
Race	0.539[c]						
White		397 (89.21)	435 (91.77)	207 (90.00)	193 (87.73)	426 (89.87)	1658 (89.96)
Black or African American		31 (6.97)	24 (5.06)	19 (8.26)	20 (9.09)	34 (7.17)	128 (6.95)
Other[d]		17 (3.82)	15 (3.16)	4 (1.74)	7 (3.18)	14 (2.95)	57 (3.09)
Height (cm)							
N		445	474	230	220	474	1843
Mean	0.656[a]	163.43	163.57	162.78	163.30	163.44	163.38
Standard deviation		6.45	6.58	6.51	6.25	6.72	6.54
Minimum - maximum		143.00-180.30	146.00-182.90	145.00-178.90	148.30-181.70	134.00-185.40	134.00-185.40
Weight (kg)							
N		445	474	230	220	474	1843
Mean	0.726[a]	69.02	69.74	70.22	69.90	69.55	69.59
Standard deviation		11.22	11.25	11.34	10.79	12.03	11.40
Minimum - maximum		43.40-105.70	41.80-106.40	45.00-98.20	45.00-104.00	39.00-105.00	39.00-106.40
BMI, (kg/m^2)							
N		445	474	230	220	474	1843
Mean	0.278[a]	25.81	26.07	26.49	26.23	25.99	26.06
Standard deviation		3.79	3.99	3.93	3.90	3.92	3.91
Minimum - maximum		17.61-39.98	16.74-35.63	17.58-34.05	18.29-34.51	16.23-34.02	16.23-39.98
Age at last menstrual period							
N		445	474	230	220	474	1843
Mean	0.851[a]	49.74	50.00	50.04	49.93	49.90	49.91
Standard deviation		4.20	3.74	3.69	4.13	3.93	3.94
Minimum - maximum		28.77-58.96	32.36-60.62	38.91-60.02	28.42-60.87	33.89-58.89	28.42-60.87

Table 8. Selected Demographic and Other Baseline Characteristics Summary (Safety Population)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=445)	BZA 20 mg/ CE 0.625 mg (n=474)	BZA 20 mg (n=230)	CE 0.45 mg/ MPA 1.5 mg (n=220)	Placebo (n=474)	Total (n=1843)
Years since last menstrual period							
N		445	474	230	220	474	1843
Mean	0.057[a]	5.20	4.41	4.54	4.73	4.80	4.75
Standard deviation		4.49	4.05	3.75	3.81	4.19	4.14
Minimum - maximum		0.51-27.65	0.51-27.43	0.55-20.57	0.52-20.00	0.53-23.80	0.51-27.65
Type of menopause	0.576[b]						
Natural		445 (100)	473 (99.79)	230 (100)	220 (100)	474 (100)	1842 (99.95)
Surgical (bilateral oophorectomy)		0	1 (0.21)	0	0	0	1 (0.05)

BMI = body mass index; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; N = number of evaluable subjects; n = number of subjects in a treatment group.

a. One-way analysis of variance with treatment as factor.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.
c. p-Value for 5 × 3 contingency table based on Chi-Square test.
d. For race, Other included American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.

Table 9. Selected Demographic and Other Baseline Characteristics Summary (Osteoporosis Substudy)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=135)	BZA 20 mg/ CE 0.625 mg (n=154)	BZA 20 mg (n=73)	CE 0.45 mg/ MPA 1.5 mg (n=70)	Placebo (n=158)	Total (n=590)
Age (years)							
N		135	154	73	70	158	590
Mean	0.746[a]	53.07	52.62	52.96	52.81	53.09	52.92
Standard deviation		3.13	3.41	3.36	4.04	3.23	3.37
Minimum - maximum		46.00-60.00	43.00-63.00	45.00-62.00	43.00-61.00	42.00-62.00	42.00-63.00
Ethnic origin	0.624[b]						
Hispanic or Latino		7 (5.19)	10 (6.49)	7 (9.59)	4 (5.71)	7 (4.43)	35 (5.93)
Non-Hispanic and Non-Latino		128 (94.81)	144 (93.51)	66 (90.41)	66 (94.29)	151 (95.57)	555 (94.07)
Race	0.794[c]						
White		124 (91.85)	146 (94.81)	69 (94.52)	62 (88.57)	145 (91.77)	546 (92.54)
Black or African American		8 (5.93)	6 (3.90)	4 (5.48)	6 (8.57)	9 (5.70)	33 (5.59)
Other[d]		3 (2.22)	2 (1.30)	0	2 (2.86)	4 (2.53)	11 (1.86)
Height (cm)							
N		135	154	73	70	158	590
Mean	0.627[a]	164.59	164.00	163.52	163.37	163.70	163.92
Standard deviation		5.88	6.68	6.09	5.91	6.31	6.23
Minimum - maximum		149.50-180.30	149.80-181.60	147.50.-177.80	151.90-177.20	145.00-180.00	145.00-181.60
Weight (kg)							
N		135	154	73	70	158	590
Mean	0.229[a]	69.61	69.08	70.97	71.44	68.41	69.53
Standard deviation		9.74	10.69	11.31	10.32	11.14	10.65
Minimum - maximum		44.50-99.80	41.80-100.00	49.50-98.20	48.00-95.20	45.50-102.10	41.80-102.10
BMI, (kg/m^2)							
N		135	154	73	70	158	590
Mean	0.059[a]	25.67	25.71	26.48	26.81	25.50	25.87
Standard deviation		3.17	3.88	3.50	3.91	3.68	3.65
Minimum - maximum		18.76-33.89	16.74-33.96	18.57-33.92	18.82-33.89	17.39-33.91	16.74-33.96
Age at last menstrual period							
N		135	154	73	70	158	590
Mean	0.832[a]	51.15	50.72	51.07	50.81	50.98	50.94
Standard deviation		3.08	3.32	3.20	3.95	3.23	3.30
Minimum - maximum		42.77-58.96	43.18-59.03	41.37-60.02	40.78-58.05	38.44-58.89	38.44-60.02

Table 9. Selected Demographic and Other Baseline Characteristics Summary (Osteoporosis Substudy)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=135)	BZA 20 mg/ CE 0.625 mg (n=154)	BZA 20 mg (n=73)	CE 0.45 mg/ MPA 1.5 mg (n=70)	Placebo (n=158)	Total (n=590)
Years since last menstrual period							
N		135	154	73	70	158	590
Mean	0.742[a]	2.42	2.43	2.43	2.49	2.63	2.49
Standard deviation		1.25	1.27	1.33	1.35	1.94	1.49
Minimum - maximum		0.51-5.41	0.46-5.04	0.55-5.31	0.53-4.97	0.53-20.87	0.46-20.87
Type of menopause							
Natural		135 (100)	154 (99.79)	73 (100)	70 (100)	158 (100)	590 (100)
Baseline T-Score							
N		135	154	73	70	158	590
Mean	0.558[a]	-0.91	-0.91	-0.82	-0.77	-0.95	-0.90
Standard deviation		0.77	0.81	0.75	0.78	0.91	0.82
Minimum - maximum		-2.40-1.50	-2.70-1.95	-2.20-0.80	2.40-1.25	-2.60-2.65	-2.70-2.65
Frax major osteoporotic score							
N		135	153	73	70	158	589
Mean	0.088[a]	5.18	5.06	4.62	4.40	4.99	4.93
Standard deviation		2.55	2.43	1.79	1.80	1.80	2.17
Minimum - maximum		1.09-17.09	1.32-14.71	1.51-8.66	1.71-10.56	1.40-10.77	1.09-17.09
Missing		0	1	0	0	0	1
Frax hip fracture score							
N		135	153	73	70	158	589
Mean	0.185[a]	0.38	0.39	0.33	0.29	0.42	0.38
Standard deviation		0.38	0.44	0.35	0.34	0.42	0.40
Minimum - maximum		0.01-2.10	0.00-2.35	0.01-1.34	0.01-1.58	0.00-2.48	0.00-2.48
Missing		0	1	0	0	0	1

BMI = body mass index; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; N = number of evaluable subjects; n = number of subjects in a treatment group.

a. One-way analysis of variance with treatment as factor.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.
c. p-Value for 5 × 3 contingency table based on Chi-Square test.
d. For race, Other included American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.

Table 10. Selected Demographic and Other Baseline Characteristics Summary (Breast Density Substudy)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=231)	BZA 20 mg/ CE 0.625 mg (n=247)	BZA 20 mg (n=122)	CE 0.45 mg/ MPA 1.5 mg (n=100)	Placebo (n=240)	Total (n=940)
Age (years)							
N		231	247	122	100	240	940
Mean	0.043[a]	54.57	53.45	54.15	53.80	54.04	54.01
Standard deviation		3.95	3.82	3.83	4.45	4.03	3.99
Minimum - maximum		43.00-64.00	43.00-64.00	46.00-63.00	43.00-64.00	41.00-64.00	41.00-64.00
Ethnic origin	0.114[b]						
Hispanic or Latino		18 (7.79)	21 (8.50)	14 (11.48)	6 (6.00)	10 (4.17)	69 (7.34)
Non-Hispanic and Non-Latino		213 (92.21)	226 (91.50)	108 (88.52)	94 (94.00)	230 (95.83)	871 (92.66)
Race	0.806[c]						
White		208 (90.04)	226 (91.50)	109 (89.34)	86 (86.00)	215 (89.58)	844 (89.79)
Black or African American		18 (7.79)	15 (6.07)	12 (9.84)	11 (11.00)	19 (7.92)	75 (7.98)
Other[d]		5 (2.16)	6 (2.43)	1 (0.82)	3 (3.00)	6 (2.50)	21 (2.23)
Height (cm)							
N		231	247	122	100	240	940
Mean	0.677[a]	163.81	163.57	163.32	163.17	164.12	163.69
Standard deviation		6.45	6.89	6.22	6.00	6.00	6.38
Minimum - maximum		146. 00-180.30	149.00-182.90	145.00-178.90	151.00-180.50	149.90-180.00	145.00-182.90
Weight (kg)							
N		231	247	122	100	240	940
Mean	0.615[a]	70.24	68.96	70.52	70.05	69.27	69.67
Standard deviation		10.88	10.88	12.39	9.77	11.96	11.25
Minimum - maximum		44.50-99.80	45.30-106.40	45.00-93.40	47.20-95.00	39.00-104.50	39.00-106.40
BMI, (kg/m^2)							
N		231	247	122	100	240	940
Mean	0.322[a]	26.16	25.80	26.39	26.34	25.69	25.99
Standard deviation		3.64	3.87	4.12	3.67	4.00	3.86
Minimum - maximum		17.61-34.64	17.70-34.31	17.58-34.05	18.63-33.73	16.23-34.01	16.23-34.64
Years since last menstrual period							
N		231	247	122	100	240	940
Mean	0.183[a]	4.80	3.93	4.58	4.48	4.48	4.43
Standard deviation		4.30	3.56	3.61	3.93	4.13	3.95
Minimum - maximum		0.52-27.65	0.51-19.74	0.55-20.57	0.53-20.00	0.53-21.73	0.51-27.65

Table 10. Selected Demographic and Other Baseline Characteristics Summary (Breast Density Substudy)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=231)	BZA 20 mg/ CE 0.625 mg (n=247)	BZA 20 mg (n=122)	CE 0.45 mg/ MPA 1.5 mg (n=100)	Placebo (n=240)	Total (n=940)
Type of menopause							
Natural		231 (100)	247 (100)	122 (100)	100 (100)	240 (100)	940 (100)
Breast density (%)							
N		190	205	101	74	199	769
Mean	0.562[a]	24.60	27.16	26.51	26.26	27.47	26.44
Standard deviation		16.79	18.78	18.69	16.63	18.47	18.00
Minimum-maximum		1.60-75.30	1.40-88.70	1.30-81.90	2.20-79.50	1.40-83.20	1.30-88.70
Missing		41	42	21	26	41	171

BMI = body mass index; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; N = number of evaluable subjects; n = number of subjects in a treatment group.

a. One-way analysis of variance with treatment as factor.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.
c. p-Value for 5 × 3 contingency table based on Chi-Square test.
d. For race, Other included American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.

Table 11. Selected Demographic and Other Baseline Characteristics Summary (Sleep Substudy)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=115)	BZA 20 mg/ CE 0.625 mg (n=123)	BZA 20 mg (n=49)	CE 0.45 mg/ MPA 1.5 mg (n=56)	Placebo (n=116)	Total (n=459)
Age (years)							
N		115	123	49	56	116	459
Mean	0.417[a]	54.00	53.17	53.12	53.16	53.36	53.42
Standard deviation		3.71	3.72	3.71	3.80	3.76	3.74
Minimum - maximum		43-62	43-64	46-62	43-61	42-64	42-64
Ethnic origin	0.168[b]						
Hispanic or Latino		7 (6.09)	7 (5.69)	6 (12.24)	7 (12.50)	5 (4.31)	32 (6.97)
Non-Hispanic and Non-Latino		108 (93.91)	116 (94.31)	43 (87.76)	49 (87.50)	111 (95.69)	427 (93.03)
Race	0.680[c]						
White		100 (86.96)	112 (91.06)	40 (81.63)	48 (85.71)	100 (86.21)	400 (87.15)
Black or African American		13 (11.30)	9 (7.32)	9 (18.37)	7 (12.50)	15 (12.93)	53 (11.55)
Other[d]		2 (1.74)	2 (1.63)	0	1 (1.79)	1 (0.86)	6 (1.31)
Height (cm)							
N		115	123	49	56	116	459
Mean	0.407[a]	163.13	164.54	163.86	163.05	163.81	163.75
Standard deviation		6.07	6.79	5.4	6.26	5.59	6.11
Minimum - maximum		146-180.3	149.8-182.9	154.9-177.8	151-180.5	153-177.8	146-182.9
Weight (kg)							
N		115	123	49	56	116	459
Mean	0.229[a]	70.27	69.13	73.4	70.19	71.1	70.5
Standard deviation		10.81	10.72	12.43	9.68	11.8	11.12
Minimum - maximum		44.5-99.8	47.7-106.4	45.4-98.2	48-91	49.1-104.5	44.5-106.4
BMI (kg/m^2)							
N		115	123	49	56	116	459
Mean	0.082[a]	26.37	25.56	27.28	26.42	26.48	26.28
Standard deviation		3.58	3.79	4.09	3.54	4.04	3.83
Minimum - maximum		19.67-33.89	19.69-34.11	18.3-33.92	18.82-33.73	17.42-34.01	17.42-34.11
Years since last menstrual period							
N		115	123	49	56	116	459
Mean	0.929[a]	3.78	3.41	3.54	3.56	3.50	3.56
Standard deviation		3.15	3.05	3.61	3.26	3.01	3.14
Minimum - maximum		0.52-18.72	0.56-18.79	0.55-20.57	0.53-18.56	0.53-20.13	0.52-20.57

Table 11. Selected Demographic and Other Baseline Characteristics Summary (Sleep Substudy)

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n=115)	BZA 20 mg/ CE 0.625 mg (n=123)	BZA 20 mg (n=49)	CE 0.45 mg/ MPA 1.5 mg (n=56)	Placebo (n=116)	Total (n=459)
Type of menopause	0.603[b]						
Natural		115 (100.00)	122 (99.19)	49 (100.00)	56 (100.0)	116 (100.0)	458 (99.78)
Surgical (bilateral oophorectomy)		0	1 (0.81)	0	0	0	1 (0.22)

BMI = body mass index; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; N = number of evaluable subjects; n = number of subjects in a treatment group.

a. One-way analysis of variance with treatment as factor.
b. p-Value for 5 × 2 contingency table based on Chi-Square test.
c. p-Value for 5 × 3 contingency table based on Chi-Square test.
d. For race, Other included American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.

Efficacy Results:

Endometrial Hyperplasia: Two (2) definitions of hyperplasia were used during the study and the results were summarized for both definitions. All endometrial biopsies were centrally read by 2 primary pathologists and if the 2 primary pathologists disagreed with respect to the presence of hyperplasia then a third pathologist was consulted. The final diagnosis based on readings from 3 pathologists could be determined in 2 ways (Definition 1 and Definition 2). For Definition 1, the outcome was determined to be hyperplasia when the 3 pathologists disagreed but at least 1 pathologist determined hyperplasia. Definition 2 required that a diagnosis of hyperplasia was made if at least 2 of the 3 pathologists agreed on the diagnosis. The observed incidence rates of endometrial hyperplasia at Month 12 and the Clopper-Pearson exact confidence limits are presented in Table 12 (hyperplasia as per Definition 2) and Table 13 (as per Definition 1).

Table 12. Incidence of Endometrial Hyperplasia at Month 12 (Definition 2, Efficacy Evaluable Population)

Treatment Group	n	Number of Subjects With Hyperplasia	Hyperplasia Rate (%)	Upper Limit	
				95% CI (1-Sided)	95% CI (2-Sided)
BZA 20 mg/CE 0.45 mg	335	1	0.30	1.41	1.65
BZA 20 mg/CE 0.625 mg	368	1	0.27	1.28	1.50
BZA 20 mg	169	0	0.00	1.76	2.16
CE 0.45 mg/MPA 1.5 mg	149	0	0.00	1.99	2.45
Placebo	354	1	0.28	1.33	1.56

BZA = bazedoxifene; CE = conjugated estrogens; CI = confidence interval; MPA = medroxyprogesterone acetate; n = number of subjects.

Table 13. Incidence of Endometrial Hyperplasia at Month 12 (Definition 1, Efficacy Evaluable Population)

Treatment Group	n	Number of Subjects With Hyperplasia	Hyperplasia Rate (%)	Upper Limit	
				95% CI (1-Sided)	95% CI (2-Sided)
BZA 20 mg/CE 0.45 mg	335	1	0.30	1.41	1.65
BZA 20 mg/CE 0.625 mg	368	2	0.54	1.70	1.95
BZA 20 mg	169	0	0.00	1.76	2.16
CE 0.45 mg/MPA 1.5 mg	149	0	0.00	1.99	2.45
Placebo	354	3	0.85	2.18	2.46

BZA = bazedoxifene; CE = conjugated estrogens; CI = confidence interval; MPA = medroxyprogesterone acetate; n = number of subjects.

Bone Mineral Density (OSS): The adjusted mean percentage changes from Baseline in the BMD of the lumbar spine at Month 6 and Month 12 compared with placebo (MITT population, LOCF analysis) are presented in Table 14.

Table 14. Adjusted Mean Percentage Changes From Baseline to Month 6 and Month 12 in the Bone Mineral Density of the Lumbar Spine (Modified Intent-to-Treat Population, LOCF)

Treatment	Time Slot	N	Adjusted % Change		Adjusted Difference vs Placebo		p-Value			
			Mean	SE	Mean	95% CI	Within Group	vs Placebo	vs BZA 20 mg	vs CE 0.45/ MPA 1.5 mg
BZA 20 mg/CE 0.45 mg	Month 6	115	0.12	0.28	0.80	(0.139, 1.470)	0.666	0.017	0.781	0.227
	Month 12	119	0.24	0.29	1.51	(0.822, 2.201)	0.423	<0.001	0.710	0.017
BZA 20 mg/CE 0.625 mg	Month 6	136	0.51	0.26	1.19	(0.556, 1.830)	0.051	<0.001	0.231	0.756
	Month 12	139	0.60	0.27	1.87	(1.209, 2.533)	0.029	<0.001	0.234	0.107
BZA 20 mg	Month 6	55	0.00	0.39	0.68	(-0.154, 1.521)	0.998	0.109	-	0.202
	Month 12	56	0.07	0.40	1.34	(0.471, 2.215)	0.867	0.002	-	0.018
CE 0.45 mg/MPA 1.5 mg	Month 6	58	0.64	0.37	1.32	(0.499, 2.147)	0.087	0.001	-	-
	Month 12	59	1.30	0.39	2.57	(1.717, 3.432)	<0.001	<0.001	-	-
Placebo	Month 6	135	-0.68	0.27	-	-	0.011	-	-	-
	Month 12	139	-1.28	0.28	-	-	<0.011	-	-	-

ANCOVA model: Percentage change from Baseline = treatment + region + baseline BMD + years since menopause.
ANCOVA = analysis of covariance; BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; CI = confidence interval; LOCF = last observation carried forward; MPA = medroxyprogesterone acetate; N = number of subjects; SE = standard error; vs = versus.

The adjusted mean percentage changes from Baseline in the BMD of the total hip at Month 6 and Month 12 compared with placebo (MITT population, LOCF analysis) are presented in Table 15.

Table 15. Adjusted Mean Percentage Changes From Baseline in the Bone Mineral Density of the Total Hip at Month 6 and Month 12 (Modified Intent-to-Treat Population, LOCF)

Treatment	Time Slot	N[a]	Adjusted % Change		Adjusted Difference vs Placebo		p-Value			
			Mean	SE	Mean	95% CI	Within Group	vs Placebo	vs BZA 20 mg	vs CE 0.45/ MPA 1.5 mg
BZA 20 mg/CE 0.45 mg	Month 6	117	0.43	0.18	1.32	(0.901, 1.742)	0.017	<0.001	0.706	0.920
	Month 12	119	0.50	0.20	1.21	(0.756, 1.671)	0.011	<0.001	0.936	0.478
BZA 20 mg/CE 0.625 mg	Month 6	136	0.66	0.17	1.56	(1.152, 1.962)	<0.001	<0.001	0.209	0.435
	Month 12	139	0.89	0.18	1.60	(1.164, 2.044)	<0.001	<0.001	0.160	0.534
BZA 20 mg	Month 6	55	0.32	0.25	1.22	(0.685, 1.750)	0.190	<0.001	-	0.680
	Month 12	56	0.47	0.27	1.19	(0.610, 1.769)	0.078	<0.001	-	0.499
CE 0.45 mg/MPA 1.5 mg	Month 6	57	0.45	0.24	1.35	(0.823, 1.875)	0.058	<0.001	-	-
	Month 12	59	0.71	0.26	1.42	(0.854, 1.994)	0.006	<0.001	-	-
Placebo	Month 6	134	-0.90	0.17	-	-	<0.001	-	-	-
	Month 12	139	-0.72	0.18	-	-	<0.001	-	-	-

ANCOVA model: Percentage change from Baseline = treatment + region + baseline BMD + years since menopause.
ANCOVA = analysis of covariance; BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; CI = confidence interval; LOCF = last observation carried forward; MPA = medroxyprogesterone acetate; SE = standard error; vs = versus.
a. Number of pairs.

Bone Turnover Markers (OSS): The median percentage changes from Baseline in serum osteocalcin, C-telopeptide, and procollagen type 1 N-propeptide (P1NP) are presented in Table 16, Table 17, and Table 18 respectively.

Table 16. Percentage Changes From Baseline in Serum Osteocalcin (Modified Intent-to-Treat Population)

Treatment	Time Slot	N	Baseline			Observed			% Change From Baseline		
			LQ	Median	UQ	LQ	Median	UQ	LQ	Median	UQ
BZA 20 mg/CE 0.45 mg											
	Month 6	115	21.15	26.21	30.70	15.88	19.35	23.80	-33.79	-25.21	-14.00
	Month 12	104	20.37	26.01	30.02	14.10	17.52	20.85	-40.77	-30.46	-18.79
BZA 20 mg/CE 0.625 mg											
	Month 6	136	20.75	27.75	33.26	15.29	19.11	23.19	-38.12	-27.79	-15.31
	Month 12	127	20.84	27.76	33.40	14.49	16.96	20.93	-46.87	-37.02	-23.50
BZA 20 mg											
	Month 6	56	19.27	23.90	30.07	17.36	20.93	25.13	-22.48	-15.60	-6.75
	Month 12	52	19.97	24.37	30.83	18.53	21.85	24.97	-33.67	-16.05	2.13
CE 0.45 mg/MPA 1.5 mg											
	Month 6	56	17.51	26.34	35.51	14.57	19.75	24.53	-38.37	-25.34	-9.65
	Month 12	50	17.94	26.62	36.12	13.47	16.31	22.17	-48.90	-32.79	-13.03
Placebo											
	Month 6	134	20.43	26.54	32.00	20.49	25.79	31.33	-15.32	-3.19	10.21
	Month 12	125	20.10	26.68	32.00	18.74	24.62	32.29	-19.29	-5.28	11.16

BZA = bazedoxifene; CE = conjugated estrogens; LQ = lower quartile (25%); MPA = medroxyprogesterone acetate; N = number of subjects; UQ = upper quartile (75%).

Table 17. Percentage Changes From Baseline in C-Telopeptide (Modified Intent-to-Treat Population)

Treatment	Time Slot	N	Baseline			Observed			% Change From Baseline		
			LQ	Median	UQ	LQ	Median	UQ	LQ	Median	UQ
BZA 20 mg/CE 0.45 mg											
	Month 6	115	2881.5	3876.0	5159.5	1640.5	2584.0	3638.0	-48.76	-34.16	-17.35
	Month 12	104	2711.5	3816.5	4730.3	1572.5	2269.5	2945.3	-55.74	-40.86	-24.04
BZA 20 mg/CE 0.625 mg											
	Month 6	136	2864.5	3799.5	5108.5	1445.0	2261.0	2856.0	-58.94	-41.41	-25.00
	Month 12	127	2703.0	3808.0	5100.0	1283.5	1955.0	2941.0	-63.47	-50.06	-29.90
BZA 20 mg											
	Month 6	56	2686.0	3867.5	4964.0	1938.0	2609.5	3616.8	-40.81	-29.37	-8.23
	Month 12	52	2686.0	3774.0	4964.0	1802.0	2868.8	3442.5	-49.55	-27.39	0.74
CE 0.45 mg/MPA 1.5 mg											
	Month 6	56	2732.8	4012.0	5546.3	1177.3	1959.3	2762.5	-68.67	-54.05	-34.66
	Month 12	50	2830.5	4050.3	5491.0	1147.5	1768.0	2771.0	-69.17	-52.56	-26.58
Placebo											
	Month 6	133	3068.5	4012.0	4938.5	2703.0	3553.0	4428.5	-26.57	-10.17	8.62
	Month 12	124	3068.5	4020.5	5044.8	2698.8	3438.3	4445.5	-30.37	-5.52	19.93

BZA = bazedoxifene; CE = conjugated estrogens; LQ = lower quartile (25%); MPA = medroxyprogesterone acetate; N = number of subjects; UQ = upper quartile (75%).

Table 18. Median Percentage Changes From Baseline in P1NP (Modified Intent-to-Treat Population)

Treatment	Time Slot	N	Baseline			Observed			% Change From Baseline		
			LQ	Median	UQ	LQ	Median	UQ	LQ	Median	UQ
BZA 20 mg/CE 0.45 mg											
	Month 6	114	44.30	57.25	76.90	31.20	39.95	52.40	-43.68	-33.73	-18.26
	Month 12	103	43.70	56.10	73.30	27.70	35.80	43.20	-49.71	-42.38	-24.16
BZA 20 mg/CE 0.625 mg											
	Month 6	135	44.70	57.80	79.70	30.40	39.10	51.70	-48.52	-30.26	-14.16
	Month 12	127	44.40	58.50	78.90	25.60	32.80	43.10	-58.66	-43.58	-24.91
BZA 20 mg											
	Month 6	57	42.30	55.30	68.50	36.50	43.80	59.00	-33.86	-17.38	-2.53
	Month 12	53	43.50	56.70	68.50	34.60	46.10	52.40	-40.42	-23.97	-7.33
CE 0.45 mg/MPA 1.5 mg											
	Month 6	56	43.45	54.90	74.00	25.70	32.90	46.15	-51.66	-39.99	-14.73
	Month 12	50	44.70	58.95	75.50	21.90	29.80	43.20	-62.91	-50.19	-20.83
Placebo											
	Month 6	133	46.60	60.30	71.70	43.60	54.70	72.10	-18.77	-5.99	12.77
	Month 12	125	46.50	60.20	71.70	42.20	50.00	63.50	-26.66	-11.13	6.60

BZA = bazedoxifene; CE = conjugated estrogens; LQ = lower quartile (25%); MPA = medroxyprogesterone acetate; N = number of subjects; P1NP = procollagen type 1 N-propeptide; UQ = upper quartile (75%).

The Ranked ANCOVA results for BTM vs placebo and BZA 20 mg separately at each time point of interest are presented in Table 19.

Table 19. Ranked ANCOVA for Bone Turnover Markers Parameters-p-Value vs Placebo and BZA 20 mg

Treatment	Time Slot	Osteocalcin vs Placebo vs BZA 20 mg	C-Telopeptide vs Placebo vs BZA 20 mg	P1NP vs Placebo vs BZA 20 mg
BZA 20 mg/CE 0.45 mg	Month 6	<0.001	<0.001	<0.001
		0.0074	0.1058	0.0029
	Month 12	<0.001	<0.001	<0.001
		<0.001	0.0024	0.0046
BZA 20 mg/CE 0.625 mg	Month 6	<0.001	<0.001	<0.001
		<0.001	<0.001	0.0043
	Month 12	<0.001	<0.001	<0.001
		<0.001	<0.001	<0.001
BZA 20 mg	Month 6	<0.001	<0.001	0.0016
	Month 12	0.0016	0.0012	<0.001
CE 0.45 mg/MPA 1.5 mg	Month 6	<0.001	<0.001	<0.001
	Month 12	<0.001	<0.001	<0.001

Ranked ANCOVA model: percentage change = treatment + region + baseline.
ANCOVA = analysis of covariance; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; P1NP = procollagen type 1 N-propeptide; vs = versus.

Sleep Substudy - Medical Outcomes Study Sleep Scale: Selected results relevant for menopausal women with bothersome VMS in the mean change from Baseline for the MOS sleep scale at Month 3 (Week 13) are presented in Table 20.

Table 20. Mean (Standard Error) Change From Baseline in the Medical Outcomes Study Sleep Scale at Month 3, Modified Intent-to-Treat Population

Sleep Subscale Questions Treatment	N	Adjusted Change Mean	 SE	p-Value vs Placebo
How long did it take you to fall asleep				
BZA 20 mg/CE 0.45 mg	110	-16.29	2.44	0.045
BZA 20 mg/CE 0.625 mg	121	-13.85	2.33	0.212
Placebo	111	-10.08	2.42	
How many hours did you sleep each night				
BZA 20 mg/CE 0.45 mg	111	0.28	0.10	0.550
BZA 20 mg/CE 0.625 mg	121	0.44	0.09	0.477
Placebo	111	0.36	0.10	
Sleep adequacy				
BZA 20 mg/CE 0.45 mg	112	14.22	2.40	0.368
BZA 20 mg/CE 0.625 mg	121	14.30	2.32	0.345
Placebo	111	11.46	2.40	
Sleep disturbance				
BZA 20 mg/CE 0.45 mg	112	-17.27	2.01	0.253
BZA 20 mg/CE 0.625 mg	121	-18.18	1.94	0.127
Placebo	111	-14.34	2.01	
Sleep problem index I				
BZA 20 mg/CE 0.45 mg	112	-13.19	1.51	0.482
BZA 20 mg/CE 0.625 mg	121	-13.99	1.46	0.254
Placebo	111	-11.84	1.50	

ANCOVA model: change = treatment + region + baseline.
ANCOVA = analysis of covariance; BZA = bazedoxifene; CE = conjugated estrogens; N = number of subjects; SE = standard error; vs = versus.

Sleep Substudy - Menopause Quality of Life Questionnaire: The mean change from Baseline to Month 3 in the MENQOL total score is summarized in Table 21. A summary of the individual MENQOL scores and change from Baseline are presented in Table 22.

Table 21. Adjusted Means in Change of Menopause-Specific Quality of Life Score (Total) and Within and Between Group Comparisons (Sleep Substudy Modified Intent-to-Treat Population)

Time Slot	Treatment	N	Adjusted Change Mean	 SE	p-Value Within Group	 vs Placebo	 vs BZA 20 mg	 vs CE 0.45 mg/ MPA 1.5 mg
Month 3	BZA 20 mg/CE 0.45 mg	110	-1.27	0.10	<0.001	0.060	<0.001	0.477
	BZA 20 mg/CE 0.625 mg	121	-1.53	0.10	<0.001	<0.001	<0.001	0.369
	BZA 20 mg	47	-0.63	0.15	<0.001	0.016		<0.001
	CE 0.45 mg/MPA 1.5 mg	52	-1.39	0.14	<0.001	0.027		
	Placebo	112	-1.03	0.10	<0.001			

ANCOVA model: change = treatment + region + baseline.
ANCOVA = analysis of covariance; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; N = number of subjects; SE = standard error; vs = versus.

Table 22. Menopause-Specific Quality of Life Score and Change From Baseline (Sleep Substudy MITT)

Test Treatment	Time Slot	N	Adjusted Change		p-Value			
			Mean	SE	Within Group	vs Placebo	vs BZA 20 mg	vs CE 0.45 mg/ MPA 1.5 mg
Vasomotor function								
BZA 20 mg/CE 0.45 mg	Month 3	111	-2.37	0.17	<0.001	<0.001	<0.001	0.003
BZA 20 mg/CE 0.625 mg	Month 3	121	-2.75	0.17	<0.001	<0.001	<0.001	0.108
BZA 20 mg	Month 3	47	-1.25	0.25	<0.001	0.475		<0.001
CE 0.45 mg/MPA 1.5 mg	Month 3	52	-3.19	0.24	<0.001	<0.001		
Placebo	Month 3	112	-1.45	0.17	<0.001			
Psychosocial function								
BZA 20 mg/CE 0.45 mg	Month 3	111	-0.67	0.12	<0.001	0.680	0.301	0.411
BZA 20 mg/CE 0.625 mg	Month 3	121	-0.84	0.12	<0.001	0.493	0.059	0.966
BZA 20 mg	Month 3	47	-0.47	0.18	0.009	0.177		0.114
CE 0.45 mg/MPA 1.5 mg	Month 3	52	-0.83	0.17	<0.001	0.621		
Placebo	Month 3	112	-0.74	0.12	<0.001			
Physical function								
BZA 20 mg/CE 0.45 mg	Month 3	111	-0.92	0.10	<0.001	0.698	0.156	0.333
BZA 20 mg/CE 0.625 mg	Month 3	121	-1.11	0.10	<0.001	0.055	0.010	0.029
BZA 20 mg	Month 3	47	-0.67	0.15	<0.001	0.262		0.673
CE 0.45 mg/MPA 1.5 mg	Month 3	52	-0.76	0.14	<0.001	0.510		
Placebo	Month 3	112	-0.87	0.10	<0.001			
Sexual function								
BZA 20 mg/CE 0.45 mg	Month 3	110	-1.20	0.16	<0.001	0.428	<0.001	0.085
BZA 20 mg/CE 0.625 mg	Month 3	121	-1.40	0.15	<0.001	0.071	<0.001	0.011
BZA 20 mg	Month 3	47	-0.09	0.23	0.715	<0.001		0.029
CE 0.45 mg/MPA 1.5 mg	Month 3	52	-0.76	0.22	<0.001	0.273		
Placebo	Month 3	112	-1.04	0.16	<0.001			

ANCOVA: change = treatment + region + baseline.
ANCOVA = analysis of covariance; BZA = bazedoxifene; CE = conjugated estrogens; MITT = modified intent-to-treat; MPA = medroxyprogesterone acetate; N = number of subjects; SE = standard error; vs = versus.

Breast Density: The adjusted mean changes from Baseline in the breast density at Month 12 compared with placebo (PP population) are presented in Table 23.

Table 23. Adjusted Mean Percentage Changes From Baseline to Month 12 in the Breast Density (Per Protocol Population)

Treatment	Time Slot	N	Adjusted % Change		Adjusted Difference vs Placebo		p-Value	
			Mean	SE	Mean	95% CI	Within Group	vs Placebo
BZA 20 mg/CE 0.45 mg	Month 12	186	-0.38	0.22	-0.06	(-0.632, 0.509)	0.092	0.832
BZA 20 mg/CE 0.625 mg	Month 12	190	-0.45	0.22	-0.13	(-0.696, 0.436)	0.044	0.651
BZA 20 mg	Month 12	97	-0.25	0.30	0.07	(-0.615, 0.758)	0.409	0.837
CE 0.45 mg/MPA 1.5 mg	Month 12	68	1.60	0.35	1.91	(1.137, 2.689)	<0.001	<0.001
Placebo	Month 12	181	-0.32	0.23			0.162	

ANCOVA model: percentage change from Baseline = treatment + region + baseline.
ANCOVA = analysis of covariance; BZA = bazedoxifene; CE = conjugated estrogens; CI = confidence interval; MPA = medroxyprogesterone acetate; N = number of subjects; SE = standard error; vs = versus.

Cumulative Amenorrhea: The cumulative number of subjects who were amenorrheic was calculated for each period in the study and is presented in Table 24.

Table 24. Number of Cumulative Amenorrhea Subjects (Modified Intent-to-Treat Population)

Treatment	4-Week Period	N	n	%	p-Value vs	
					Placebo	CE/MPA
BZA 20 mg/CE 0.45 mg	1st - 13th	355	312	87.89	0.138	<0.001
	2nd- 13th	356	317	89.04		
	3rd - 13th	356	322	90.45		
	4th - 13th	356	324	91.01		
	5th - 13th	356	327	91.85		
	6th - 13th	356	329	92.42		
	7th - 13th	356	335	94.10	0.074	<0.001
	8th - 13th	356	338	94.94		
	9th - 13th	356	342	96.07		
	10th - 13th	357	344	96.36		
	11th - 13th	357	347	97.20		
	12th - 13th	357	350	98.04		
	13th - 13th	357	351	98.32	1.000	<0.001
BZA 20 mg/CE 0.625 mg	1st - 13th	390	331	84.87	0.765	<0.001
	2nd - 13th	390	339	86.92		
	3rd - 13th	390	347	88.97		
	4th - 13th	391	353	90.28		
	5th - 13th	391	358	91.56		
	6th - 13th	391	360	92.07		
	7th - 13th	391	364	93.09	0.236	<0.001
	8th - 13th	392	366	93.37		
	9th - 13th	392	369	94.13		
	10th - 13th	392	371	94.64		
	11th - 13th	392	379	96.68		
	12th - 13th	392	380	96.94		
	13th - 13th	392	387	98.72	0.769	<0.001
BZA 20 mg	1st - 13th	187	154	82.35	0.633	<0.001
	2nd - 13th	187	162	86.63		
	3rd - 13th	187	167	89.30		
	4th - 13th	187	170	90.91		
	5th - 13th	187	171	91.44		
	6th - 13th	187	174	93.05		
	7th - 13th	187	177	94.65	0.102	<0.001
	8th - 13th	187	178	95.19		
	9th - 13th	187	179	95.72		
	10th - 13th	187	182	97.33		
	11th - 13th	187	184	98.40		
	12th - 13th	187	184	98.40		
	13th - 13th	187	185	98.93	1.000	<0.001
CE 0.45 mg/MPA 1.5 mg	1st - 13th	158	86	54.43	<0.001	
	2nd - 13th	158	91	57.59		
	3rd - 13th	158	95	60.13		
	4th - 13th	159	103	64.78		
	5th - 13th	159	109	68.55		
	6th - 13th	159	111	69.81		
	7th - 13th	159	117	73.58	<0.001	
	8th - 13th	159	121	76.10		
	9th - 13th	159	122	76.73		
	10th - 13th	159	125	78.62		
	11th - 13th	159	129	81.13		

Table 24. Number of Cumulative Amenorrhea Subjects (Modified Intent-to-Treat Population)

Treatment	4-Week Period	N	n	%	p-Value vs	
					Placebo	CE/MPA
Placebo	12th - 13th	159	133	83.65		
	13th - 13th	159	145	91.19	<0.001	
	1st - 13th	379	318	83.91		
	2nd - 13th	379	325	85.75		
	3rd - 13th	379	328	86.54		
	4th - 13th	380	337	88.68		
	5th - 13th	380	338	88.95		
	6th - 13th	380	342	90.00		
	7th - 13th	380	344	90.53		
	8th - 13th	380	350	92.11		
	9th - 13th	380	352	92.63		
	10th - 13th	380	355	93.42		
	11th - 13th	380	367	96.58		
	12th - 13th	380	370	97.37		
	13th - 13th	380	374	98.42		

p-Values from Fisher's Exact test.
BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; N = total number of subjects; n = number of subjects with cumulative amenorrhea; vs = versus.

The noncumulative amenorrhea profile is presented in Table 25.

Table 25. Noncumulative Amenorrhea Profile (Modified Intent-to-Treat Population, 4-Week Interval)

Treatment	Time Slot	Total Number of Subjects	Bleeding/Spotting				
			Number	%	p-Value vs Placebo	p-Value vs CE/MPA	Mean Days
BZA 20 mg/CE 0.45 mg	Week 1-4	440	17	3.86	0.624	<0.001	0.20
	Week 5-8	428	19	4.44	0.868	<0.001	0.26
	Week 9-12	417	9	2.16	0.087	<0.001	0.14
	Week 13-16	415	10	2.41	0.425	<0.001	0.11
	Week 17-20	399	9	2.26	0.307	<0.001	0.08
	week 21-24	395	11	2.78	0.689	<0.001	0.15
	Week 25-28	393	8	2.04	0.285	<0.001	0.11
	Week 29-32	376	6	1.60	1.000	<0.001	0.11
	Week 33-36	373	2	0.54	0.065	<0.001	0.04
	Week 37-40	373	6	1.61	0.014	<0.001	0.08
	Week 41-44	363	5	1.38	1.000	<0.001	0.14
	Week 45-48	358	3	0.84	0.226	<0.001	0.12
	Week 49-52	357	6	1.68	1.000	<0.001	0.15
BZA 20 mg/CE 0.625 mg	Week 1-4	468	29	6.20	0.317	<0.001	0.23
	Week 5-8	458	23	5.02	0.531	<0.001	0.30
	Week 9-12	451	16	3.55	0.610	<0.001	0.27
	Week 13-16	446	13	2.91	0.848	<0.001	0.16
	Week 17-20	426	11	2.58	0.551	<0.001	0.12
	week 21-24	424	9	2.12	0.300	<0.001	0.19
	Week 25-28	422	9	2.13	0.299	<0.001	0.15
	Week 29-32	416	7	1.68	1.000	<0.001	0.15
	Week 33-36	413	12	2.91	0.660	<0.001	0.21
	Week 37-40	411	12	2.92	0.199	<0.001	0.20
	Week 41-44	396	5	1.26	0.770	<0.001	0.09
	Week 45-48	394	9	2.28	1.000	<0.001	0.11
	Week 49-52	392	5	1.28	0.769	<0.001	0.11
BZA 20 mg	Week 1-4	229	13	5.68	0.582	<0.001	0.17
	Week 5-8	221	8	3.62	0.836	<0.001	0.24
	Week 9-12	217	6	2.76	0.394	<0.001	0.05
	Week 13-16	213	7	3.29	1.000	<0.001	0.06
	Week 17-20	201	5	2.49	0.629	<0.001	0.05
	week 21-24	199	4	2.01	0.450	<0.001	0.08
	Week 25-28	197	2	1.02	0.107	<0.001	0.03
	Week 29-32	194	3	1.55	1.000	<0.001	0.06
	Week 33-36	192	4	2.08	1.000	<0.001	0.06
	Week 37-40	191	3	1.57	0.063	<0.001	0.02
	Week 41-44	188	0	0.00	0.184	<0.001	0.00
	Week 45-48	188	1	0.53	0.283	<0.001	0.01
	Week 49-52	187	2	1.07	1.000	<0.001	0.01
CE 0.45 mg/MPA 1.5 mg	Week 1-4	216	45	20.83	<0.001		1.15
	Week 5-8	205	50	24.39	<0.001		1.78
	Week 9-12	199	51	25.63	<0.001		1.78
	Week 13-16	196	48	24.49	<0.001		1.77
	Week 17-20	184	34	18.48	<0.001		1.24
	week 21-24	183	34	18.58	<0.001		1.02
	Week 25-28	182	27	14.84	<0.001		1.01
	Week 29-32	173	21	12.14	<0.001		0.84
	Week 33-36	170	22	12.94	<0.001		0.76
	Week 37-40	168	24	14.29	<0.001		1.11
	Week 41-44	162	22	13.58	<0.001		1.34
	Week 45-48	160	23	14.38	<0.001		0.93
	Week 49-52	159	14	8.81	<0.001		0.53
Placebo	Week 1-4	470	22	4.68			0.16
	Week 5-8	462	19	4.11			0.26

Table 25. Noncumulative Amenorrhea Profile (Modified Intent-to-Treat Population, 4-Week Interval)

Treatment	Time Slot	Total Number of Subjects	Bleeding/Spotting				
			Number	%	p-Value vs Placebo	p-Value vs CE/MPA	Mean Days
	Week 9-12	452	20	4.42			0.26
	Week 13-16	446	15	3.36			0.21
	Week 17-20	427	15	3.51			0.18
	week 21-24	423	14	3.31			0.17
	Week 25-28	420	14	3.33			0.23
	Week 29-32	405	7	1.73			0.12
	Week 33-36	399	9	2.26			0.19
	Week 37-40	394	19	4.82			0.25
	Week 41-44	386	6	1.55			0.13
	Week 45-48	383	8	2.09			0.19
	Week 49-52	380	6	1.58			0.13

p-Value from Fishers Exact test.
BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; vs = versus.

The number and percentage of subjects reported at least 1 day of breast tenderness during each 4-week period for 1-year of therapy is presented in Table 26.

Table 26. Summary of Subjects Reporting at Least 1 Day of Breast Tenderness (MITT Population)

Treatment	Time Slot	Number of Subjects	Number of Breast Tenderness	Percent of Breast Tenderness	p-Values	
					Placebo	CE/MPA
BZA 20 mg/CE 0.45 mg	Screening	429	27	6.29	-	-
	Week 1-4	426	40	9.39	0.546	<0.001
	Week 5-8	423	34	8.04	0.821	<0.001
	Week 9-12	412	24	5.83	0.698	<0.001
	Week 13-16	411	29	7.06	0.446	<0.001
	Week 17-20	395	16	4.05	0.892	<0.001
	Week 21-24	391	18	4.60	0.810	<0.001
	Week 25-28	389	12	3.08	0.473	<0.001
	Week 29-32	372	17	4.57	0.030	<0.001
	Week 33-36	369	11	2.98	0.453	<0.001
	Week 37-40	369	15	4.07	0.391	<0.001
	Week 41-44	359	13	3.62	0.407	0.008
	Week 45-48	354	13	3.67	0.644	0.002
	Week 49-52	353	11	3.12	0.666	0.002
BZA 20 mg/CE 0.625 mg	Screening	449	29	6.46	-	-
	Week 1-4	449	41	9.13	0.641	<0.001
	Week 5-8	447	31	6.94	0.361	<0.001
	Week 9-12	439	35	7.97	0.100	<0.001
	Week 13-16	433	36	8.31	0.142	<0.001
	Week 17-20	412	18	4.37	0.906	<0.001
	Week 21-24	410	16	3.90	0.798	<0.001
	Week 25-28	409	23	5.62	0.258	<0.001
	Week 29-32	403	16	3.97	0.058	<0.001
	Week 33-36	401	14	3.49	0.230	<0.001
	Week 37-40	399	16	4.01	0.360	<0.001
	Week 41-44	384	10	2.60	0.892	<0.001
	Week 45-48	382	12	3.14	0.912	<0.001
	Week 49-52	380	11	2.89	0.791	0.001
BZA 20 mg	Screening	220	10	4.55	-	-
	Week 1-4	220	13	5.91	0.348	<0.001
	Week 5-8	216	17	7.87	0.898	<0.001
	Week 9-12	212	14	6.60	0.438	<0.001
	Week 13-16	208	18	8.65	0.145	<0.001
	Week 17-20	197	12	6.09	0.282	0.001
	Week 21-24	195	11	5.64	0.414	0.005
	Week 25-28	193	8	4.15	0.810	<0.001
	Week 29-32	190	3	1.58	0.943	<0.001
	Week 33-36	188	6	3.19	0.273	0.001
	Week 37-40	187	5	2.67	0.934	0.001
	Week 41-44	184	3	1.63	0.561	0.003
	Week 45-48	184	4	2.17	0.593	0.002
	Week 49-52	183	3	1.64	0.505	0.002
CE 0.45 mg/MPA 1.5 mg	Screening	206	15	7.28	-	-
	Week 1-4	205	42	20.49	<0.001	-
	Week 5-8	202	49	24.26	<0.001	-
	Week 9-12	196	47	23.98	<0.001	-
	Week 13-16	193	41	21.24	<0.001	-
	Week 17-20	181	31	17.13	<0.001	-
	Week 21-24	180	27	15.00	<0.001	-

Table 26. Summary of Subjects Reporting at Least 1 Day of Breast Tenderness (MITT Population)

Treatment	Time Slot	Number of Subjects	Number of Breast Tenderness	Percent of Breast Tenderness	p-Values	
					Placebo	CE/MPA
	Week 25-28	179	28	15.64	<0.001	-
	Week 29-32	171	26	15.20	<0.001	-
	Week 33-36	168	21	12.50	<0.001	-
	Week 37-40	166	20	12.05	<0.001	-
	Week 41-44	159	15	9.43	<0.001	-
	Week 45-48	157	17	10.83	<0.001	-
	Week 49-52	156	15	9.62	<0.001	-
Placebo	Screening	457	30	6.56	-	-
	Week 1-4	457	38	8.32	-	-
	Week 5-8	456	39	8.55	-	-
	Week 9-12	447	24	5.37	-	-
	Week 13-16	440	26	5.91	-	-
	Week 17-20	420	18	4.29	-	-
	Week 21-24	416	18	4.33	-	-
	Week 25-28	416	17	4.09	-	-
	Week 29-32	401	8	2.00	-	-
	Week 33-36	395	9	2.28	-	-
	Week 37-40	390	12	3.08	-	-
	Week 41-44	382	10	2.62	-	-
	Week 45-48	379	12	3.17	-	-
	Week 49-52	376	10	2.66	-	-

p-Value: Cochran-Mantel-Haenszel sasname: baseline treat proportion.
BZA = bazedoxifene; CE = conjugated estrogens; MITT = modified intention-to-treat; MPA = medroxy progesterone acetate.

Safety Results: The non-serious AEs with an incidence ≥2% are presented by treatment group in Table 27.

Vaginal hemorrhage was the only treatment-related AE observed with incidence ≥2% in any treatment group (reported by 2.3% of subjects in the CE 0.45 mg/MPA 1.5 mg group).

Table 27. Number (%) of Subjects Reporting Percentages ≥2% Non-Serious MedDRA Adverse Events

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Any AEs	0.841	407 (91.5)	426 (89.9)	207 (90.0)	197 (89.5)	423 (89.2)	1660 (90.1)
Blood and lymphatic system disorders	0.191	2 (0.4)	6 (1.3)	3 (1.3)	6 (2.7)	7 (1.5)	24 (1.3)
Cardiac disorders	0.442	8 (1.8)	8 (1.7)	1 (0.4)	5 (2.3)	5 (1.1)	27 (1.5)
Ear and labyrinth disorders	0.750	16 (3.6)	14 (3.0)	6 (2.6)	6 (2.7)	10 (2.1)	52 (2.8)
Eye disorders	0.415	13 (2.9)	21 (4.4)	4 (1.7)	7 (3.2)	15 (3.2)	60 (3.3)
Gastrointestinal disorders	0.223	169 (38.0)	167 (35.2)	79 (34.3)	76 (34.5)	145 (30.6)	636 (34.5)
Abdominal discomfort	0.873	11 (2.5)	13 (2.7)	8 (3.5)	6 (2.7)	10 (2.1)	48 (2.6)
Abdominal distension	0.806	9 (2.0)	13 (2.7)	4 (1.7)	7 (3.2)	13 (2.7)	46 (2.5)
Abdominal pain	0.791	23 (5.2)	34 (7.2)	15 (6.5)	13 (5.9)	31 (6.5)	116 (6.3)
Abdominal pain lower	0.014*	5 (1.1)	5 (1.1)	6 (2.6)	8 (3.6)	3 (0.6)	27 (1.5)
Abdominal pain upper	0.819	21 (4.7)	21 (4.4)	7 (3.0)	9 (4.1)	17 (3.6)	75 (4.1)
Constipation	0.676	20 (4.5)	25 (5.3)	14 (6.1)	14 (6.4)	20 (4.2)	93 (5.0)
Diarrhoea	0.626	33 (7.4)	26 (5.5)	13 (5.7)	13 (5.9)	24 (5.1)	109 (5.9)
Dyspepsia	0.181	24 (5.4)	13 (2.7)	9 (3.9)	11 (5.0)	14 (3.0)	71 (3.9)
Flatulence	0.491	13 (2.9)	9 (1.9)	2 (0.9)	4 (1.8)	11 (2.3)	39 (2.1)
Gastritis	0.202	4 (0.9)	2 (0.4)	5 (2.2)	2 (0.9)	3 (0.6)	16 (0.9)
Gastrooesophageal reflux disease	0.015*	4 (0.9)	4 (0.8)	1 (0.4)	0	12 (2.5)	21 (1.1)
Nausea	0.367	32 (7.2)	29 (6.1)	8 (3.5)	11 (5.0)	26 (5.5)	106 (5.8)
Toothache	0.894	21 (4.7)	20 (4.2)	8 (3.5)	8 (3.6)	17 (3.6)	74 (4.0)
Vomiting	0.890	14 (3.1)	10 (2.1)	7 (3.0)	6 (2.7)	12 (2.5)	49 (2.7)
General disorders and administration site conditions	0.652	68 (15.3)	80 (16.9)	36 (15.7)	27 (12.3)	73 (15.4)	284 (15.4)
Fatigue	0.946	12 (2.7)	12 (2.5)	7 (3.0)	4 (1.8)	12 (2.5)	47 (2.6)
Oedema peripheral	0.400	10 (2.2)	4 (0.8)	3 (1.3)	4 (1.8)	5 (1.1)	26 (1.4)
Pain	0.439	20 (4.5)	24 (5.1)	16 (7.0)	7 (3.2)	22 (4.6)	89 (4.8)
Pyrexia	0.808	10 (2.2)	10 (2.1)	5 (2.2)	5 (2.3)	6 (1.3)	36 (2.0)
Immune system disorders	0.999	16 (3.6)	18 (3.8)	8 (3.5)	8 (3.6)	18 (3.8)	68 (3.7)
Seasonal allergy	0.664	14 (3.1)	14 (3.0)	4 (1.7)	6 (2.7)	9 (1.9)	47 (2.6)
Infections and infestations	0.462	236 (53.0)	232 (48.9)	108 (47.0)	105 (47.7)	227 (47.9)	908 (49.3)
Bronchitis	0.504	8 (1.8)	14 (3.0)	8 (3.5)	9 (4.1)	14 (3.0)	53 (2.9)
Cystitis	0.414	10 (2.2)	11 (2.3)	8 (3.5)	6 (2.7)	6 (1.3)	41 (2.2)
Ear infection	0.110	3 (0.7)	6 (1.3)	1 (0.4)	6 (2.7)	4 (0.8)	20 (1.1)
Gastroenteritis	0.454	3 (0.7)	5 (1.1)	4 (1.7)	5 (2.3)	7 (1.5)	24 (1.3)

Table 27. Number (%) of Subjects Reporting Percentages ≥2% Non-Serious MedDRA Adverse Events

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Influenza	0.635	27 (6.1)	30 (6.3)	18 (7.8)	13 (5.9)	23 (4.9)	111 (6.0)
Nasopharyngitis	0.039*	91 (20.4)	72 (15.2)	44 (19.1)	32 (14.5)	65 (13.7)	304 (16.5)
Sinusitis	0.421	42 (9.4)	37 (7.8)	19 (8.3)	12 (5.5)	33 (7.0)	143 (7.8)
Tooth infection	0.865	8 (1.8)	11 (2.3)	6 (2.6)	3 (1.4)	11 (2.3)	39 (2.1)
Upper respiratory tract infection	0.222	36 (8.1)	38 (8.0)	9 (3.9)	13 (5.9)	30 (6.3)	126 (6.8)
Urinary tract infection	0.055	30 (6.7)	20 (4.2)	14 (6.1)	5 (2.3)	33 (7.0)	102 (5.5)
Injury, poisoning and procedural complications	0.731	85 (19.1)	84 (17.7)	45 (19.6)	44 (20.0)	101 (21.3)	359 (19.5)
Contusion	0.066	7 (1.6)	3 (0.6)	4 (1.7)	4 (1.8)	15 (3.2)	33 (1.8)
Muscle strain	0.309	7 (1.6)	9 (1.9)	8 (3.5)	5 (2.3)	16 (3.4)	45 (2.4)
Post procedural haemorrhage	0.823	9 (2.0)	8 (1.7)	4 (1.7)	5 (2.3)	13 (2.7)	39 (2.1)
Procedural pain	0.142	26 (5.8)	36 (7.6)	6 (2.6)	14 (6.4)	30 (6.3)	112 (6.1)
Investigations	0.307	46 (10.3)	56 (11.8)	24 (10.4)	33 (15.0)	65 (13.7)	224 (12.2)
Blood cholesterol increased	0.143	10 (2.2)	5 (1.1)	7 (3.0)	1 (0.5)	7 (1.5)	30 (1.6)
Gamma-glutamyltransferase increased	0.109	10 (2.2)	3 (0.6)	2 (0.9)	2 (0.9)	3 (0.6)	20 (1.1)
Low density lipoprotein increased	0.294	4 (0.9)	3 (0.6)	5 (2.2)	1 (0.5)	4 (0.8)	17 (0.9)
Weight increased	0.240	11 (2.5)	13 (2.7)	5 (2.2)	9 (4.1)	22 (4.6)	60 (3.3)
Metabolism and nutrition disorders	0.107	22 (4.9)	9 (1.9)	11 (4.8)	10 (4.5)	16 (3.4)	68 (3.7)
Musculoskeletal and connective tissue disorders	0.663	179 (40.2)	201 (42.4)	91 (39.6)	80 (36.4)	188 (39.7)	739 (40.1)
Arthralgia	0.967	42 (9.4)	49 (10.3)	22 (9.6)	19 (8.6)	47 (9.9)	179 (9.7)
Arthritis	0.018*	4 (0.9)	2 (0.4)	5 (2.2)	0	1 (0.2)	12 (0.7)
Back pain	0.831	52 (11.7)	64 (13.5)	29 (12.6)	25 (11.4)	65 (13.7)	235 (12.8)
Muscle spasms	0.106	48 (10.8)	45 (9.5)	26 (11.3)	14 (6.4)	33 (7.0)	166 (9.0)
Musculoskeletal pain	0.364	31 (7.0)	34 (7.2)	10 (4.3)	9 (4.1)	31 (6.5)	115 (6.2)
Myalgia	0.335	32 (7.2)	28 (5.9)	21 (9.1)	13 (5.9)	25 (5.3)	119 (6.5)
Neck pain	0.743	21 (4.7)	23 (4.9)	9 (3.9)	6 (2.7)	20 (4.2)	79 (4.3)
Pain in extremity	0.197	45 (10.1)	46 (9.7)	17 (7.4)	31 (14.1)	45 (9.5)	184 (10.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.385	8 (1.8)	9 (1.9)	5 (2.2)	9 (4.1)	10 (2.1)	41 (2.2)
Nervous system disorders	0.659	132 (29.7)	150 (31.6)	67 (29.1)	75 (34.1)	156 (32.9)	580 (31.5)
Dizziness	0.679	17 (3.8)	16 (3.4)	7 (3.0)	9 (4.1)	11 (2.3)	60 (3.3)
Headache	0.509	96 (21.6)	109 (23.0)	48 (20.9)	54 (24.5)	122 (25.7)	429 (23.3)
Migraine	0.769	7 (1.6)	8 (1.7)	5 (2.2)	3 (1.4)	12 (2.5)	35 (1.9)

Table 27. Number (%) of Subjects Reporting Percentages ≥2% Non-Serious MedDRA Adverse Events

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Sinus headache	0.995	12 (2.7)	14 (3.0)	7 (3.0)	7 (3.2)	15 (3.2)	55 (3.0)
Psychiatric disorders	0.629	61 (13.7)	63 (13.3)	27 (11.7)	22 (10.0)	55 (11.6)	228 (12.4)
Anxiety	0.458	9 (2.0)	16 (3.4)	4 (1.7)	7 (3.2)	9 (1.9)	45 (2.4)
Depression	0.817	13 (2.9)	9 (1.9)	6 (2.6)	5 (2.3)	9 (1.9)	42 (2.3)
Insomnia	0.888	27 (6.1)	25 (5.3)	15 (6.5)	12 (5.5)	32 (6.8)	111 (6.0)
Renal and urinary disorders	0.736	15 (3.4)	18 (3.8)	11 (4.8)	6 (2.7)	21 (4.4)	71 (3.9)
Haematuria	0.179	6 (1.3)	5 (1.1)	7 (3.0)	1 (0.5)	8 (1.7)	27 (1.5)
Reproductive system and breast disorders	<0.001***	109 (24.5)	111 (23.4)	41 (17.8)	87 (39.5)	103 (21.7)	451 (24.5)
Breast pain	0.080	4 (0.9)	11 (2.3)	2 (0.9)	4 (1.8)	2 (0.4)	23 (1.2)
Breast tenderness	<0.001***	17 (3.8)	19 (4.0)	5 (2.2)	26 (11.8)	18 (3.8)	85 (4.6)
Metrorrhagia	0.059	5 (1.1)	5 (1.1)	2 (0.9)	8 (3.6)	6 (1.3)	26 (1.4)
Pelvic pain	0.400	6 (1.3)	8 (1.7)	1 (0.4)	6 (2.7)	8 (1.7)	29 (1.6)
Uterine haemorrhage	0.021*	2 (0.4)	5 (1.1)	1 (0.4)	7 (3.2)	5 (1.1)	20 (1.1)
Uterine spasm	0.421	11 (2.5)	6 (1.3)	6 (2.6)	7 (3.2)	8 (1.7)	38 (2.1)
Vaginal discharge	0.630	6 (1.3)	7 (1.5)	2 (0.9)	4 (1.8)	11 (2.3)	30 (1.6)
Vaginal haemorrhage	<0.001***	30 (6.7)	29 (6.1)	14 (6.1)	37 (16.8)	36 (7.6)	146 (7.9)
Respiratory, thoracic and mediastinal disorders	0.240	81 (18.2)	79 (16.7)	34 (14.8)	48 (21.8)	74 (15.6)	316 (17.1)
Cough	0.780	24 (5.4)	30 (6.3)	10 (4.3)	11 (5.0)	30 (6.3)	105 (5.7)
Nasal congestion	0.378	15 (3.4)	8 (1.7)	9 (3.9)	6 (2.7)	11 (2.3)	49 (2.7)
Oropharyngeal pain	0.012*	25 (5.6)	26 (5.5)	12 (5.2)	22 (10.0)	16 (3.4)	101 (5.5)
Sinus congestion	0.356	13 (2.9)	21 (4.4)	4 (1.7)	7 (3.2)	13 (2.7)	58 (3.1)
Skin and subcutaneous tissue disorders	0.048*	64 (14.4)	76 (16.0)	34 (14.8)	38 (17.3)	48 (10.1)	260 (14.1)
Alopecia	0.884	9 (2.0)	9 (1.9)	3 (1.3)	4 (1.8)	6 (1.3)	31 (1.7)
Night sweats	0.484	5 (1.1)	12 (2.5)	4 (1.7)	6 (2.7)	12 (2.5)	39 (2.1)
Rash	0.200	8 (1.8)	15 (3.2)	4 (1.7)	6 (2.7)	5 (1.1)	38 (2.1)
Vascular disorders	0.428	42 (9.4)	50 (10.5)	25 (10.9)	16 (7.3)	56 (11.8)	189 (10.3)
Hot flush	0.348	27 (6.1)	37 (7.8)	20 (8.7)	11 (5.0)	40 (8.4)	135 (7.3)
Hypertension	0.605	15 (3.4)	9 (1.9)	4 (1.7)	6 (2.7)	13 (2.7)	47 (2.6)

Table 27. Number (%) of Subjects Reporting Percentages ≥2% Non-Serious MedDRA Adverse Events

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843

Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
Classifications of AEs are based on the MedDRA.
Overall p-value: refers to number of subjects data. p-Value for Chi-Square.
AEs = adverse events; BZA = bazedoxifene; CE = conjugated estrogens; MedDRA = Medical Dictionary for Regulatory Activities;
MPA = medroxyprogesterone acetate; n = number of subjects in a treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

The number of subjects with SAEs is presented by treatment group in Table 28. The number of subjects with treatment-related SAEs is presented by treatment group in Table 29.

Table 28. Number (%) of Subjects With Serious Adverse Events Reported in Any Treatment Group

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Any adverse event	0.343	16 (3.6)	17 (3.6)	5 (2.2)	13 (5.9)	18 (3.8)	69 (3.7)
Blood and lymphatic system disorders	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Leukocytosis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Cardiac disorders	0.461	1 (0.2)	1 (0.2)	0	0	3 (0.6)	5 (0.3)
Angina pectoris	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Arteriosclerosis coronary artery	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Atrial fibrillation	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Myocardial infarction	0.733	1 (0.2)	0	0	0	1 (0.2)	2 (0.1)
Congenital, familial and genetic disorders	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Atrial septal defect	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Ear and labyrinth disorders	0.914	1 (0.2)	1 (0.2)	0	0	1 (0.2)	3 (0.2)
Acute vestibular syndrome	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Vertigo	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Vertigo positional	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Endocrine disorders	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Autoimmune thyroiditis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Gastrointestinal disorders	0.858	1 (0.2)	2 (0.4)	1 (0.4)	0	1 (0.2)	5 (0.3)
Abdominal pain upper	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Colitis ulcerative	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Duodenitis	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Erosive oesophagitis	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Gastritis	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Gastritis erosive	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Gastrointestinal haemorrhage	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Ileus	0.135	0	0	1 (0.4)	0	0	1 (0.1)
General disorders and administration site conditions	0.295	1 (0.2)	0	1 (0.4)	2 (0.9)	1 (0.2)	5 (0.3)
Non-cardiac chest pain	0.716	1 (0.2)	0	1 (0.4)	1 (0.5)	1 (0.2)	4 (0.2)
Pyrexia	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Hepatobiliary disorders	0.665	0	1 (0.2)	0	1 (0.5)	1 (0.2)	3 (0.2)
Cholecystitis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Cholecystitis acute	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Cholelithiasis	0.576	0	1 (0.2)	0	0	0	1 (0.1)

Table 28. Number (%) of Subjects With Serious Adverse Events Reported in Any Treatment Group

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Infections and infestations	0.582	1 (0.2)	2 (0.4)	2 (0.9)	0	3 (0.6)	8 (0.4)
Appendicitis	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Cellulitis	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Diverticulitis	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Lyme disease	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Pneumonia	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Pneumonia bacterial	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Pyelonephritis	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Injury, poisoning and procedural complications	0.833	1 (0.2)	2 (0.4)	2 (0.9)	1 (0.5)	2 (0.4)	8 (0.4)
Clavicle fracture	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Contusion	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Head injury	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Humerus fracture	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Muscle rupture	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Patella fracture	0.412	0	0	1 (0.4)	0	1 (0.2)	2 (0.1)
Procedural pain	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Road traffic accident	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Thoracic vertebral fracture	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Traumatic lung injury	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Investigations	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Alanine aminotransferase increased	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Aspartate aminotransferase increased	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Metabolism and nutrition disorders	0.185	0	0	1 (0.4)	1 (0.5)	0	2 (0.1)
Dehydration	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Hypoglycaemia	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0.523	2 (0.4)	1 (0.2)	0	1 (0.5)	0	4 (0.2)
Intervertebral disc protrusion	0.179	2 (0.4)	0	0	0	0	2 (0.1)
Osteosclerosis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Pain in extremity	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.352	7 (1.6)	4 (0.8)	2 (0.9)	6 (2.7)	7 (1.5)	26 (1.4)
Basal cell carcinoma	0.537	2 (0.4)	2 (0.4)	1 (0.4)	3 (1.4)	2 (0.4)	10 (0.5)

Table 28. Number (%) of Subjects With Serious Adverse Events Reported in Any Treatment Group

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Benign fallopian tube neoplasm	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Breast cancer	0.733	1 (0.2)	0	0	0	1 (0.2)	2 (0.1)
Breast cancer metastatic	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Breast cancer stage	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Colon cancer stage IV	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Hepatic cancer metastatic	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Hodgkin's disease	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Lung cancer metastatic	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Malignant melanoma	0.719	2 (0.4)	1 (0.2)	0	0	1 (0.2)	4 (0.2)
Metastases to spine	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Salivary gland adenoma	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Squamous cell carcinoma	0.371	1 (0.2)	0	0	1 (0.5)	0	2 (0.1)
Squamous cell carcinoma of skin	0.914	1 (0.2)	1 (0.2)	0	0	1 (0.2)	3 (0.2)
Nervous system disorders	0.564	0	2 (0.4)	0	1 (0.5)	1 (0.2)	4 (0.2)
Cerebrovascular accident	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Complex partial seizures	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Migraine	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Migraine with aura	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Psychiatric disorders	0.756	0	1 (0.2)	0	0	1 (0.2)	2 (0.1)
Anxiety	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Anxiety disorder	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Depression	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Renal and urinary disorders	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Nephrolithiasis	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Haemoptysis	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Urticaria	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Vascular disorders	0.048*	1 (0.2)	0	0	2 (0.9)	0	3 (0.2)
Circulatory collapse	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Deep vein thrombosis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Hypertensive emergency	0.117	0	0	0	1 (0.5)	0	1 (0.1)

Table 28. Number (%) of Subjects With Serious Adverse Events Reported in Any Treatment Group

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Overall p-value: refers to number of subjects data. p-Value for Chi-Square.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
BZA = bazedoxifene; CE = conjugated estrogens; IV = intravenous; MPA = medroxyprogesterone acetate; n = number of subjects in a treatment group.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

Table 29. Number (%) of Subjects With Treatment-Related Serious Adverse Events

System Organ Class[a] Preferred Term	Treatment					
	BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Any adverse event	1 (0.2)	2 (0.4)	0	3 (1.4)	2 (0.4)	8 (0.4)
Hepatobiliary disorders	0	0	0	1 (0.5)	1 (0.2)	2 (0.1)
Cholecystitis	0	0	0	1 (0.5)	0	1 (0.1)
Cholecystitis acute	0	0	0	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.2)	0	0	1 (0.5)	1 (0.2)	3 (0.2)
Breast cancer	0	0	0	0	1 (0.2)	1 (0.1)
Breast cancer metastatic	1 (0.2)	0	0	0	0	1 (0.1)
Breast cancer stage II	0	0	0	1 (0.5)	0	1 (0.1)
Nervous system disorders	0	2 (0.4)	0	0	0	2 (0.1)
Cerebrovascular accident	0	1 (0.2)	0	0	0	1 (0.1)
Migraine with aura	0	1 (0.2)	0	0	0	1 (0.1)
Vascular disorders	0	0	0	1 (0.5)	0	1 (0.1)
Deep vein thrombosis	0	0	0	1 (0.5)	0	1 (0.1)

Classifications of adverse events are based on the MedDRA.
BZA = bazedoxifene; CE = conjugated estrogens; MedDRA = Medical Dictionary for Regulatory Activities; MPA = medroxyprogesterone acetate; n = number of subjects in a treatment group.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

Table 30 summarizes the AEs that were cited as reasons for prematurely discontinuing from the study in any treatment group.

Table 30. Number (%) of Subjects Reporting MedDRA Adverse Events Resulting in Withdrawal From the Study for the Subjects

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Any adverse event	0.012*	34 (7.6)	33 (7.0)	16 (7.0)	31 (14.1)	33 (7.0)	147 (8.0)
Cardiac disorders	0.215	1 (0.2)	3 (0.6)	0	0	0	4 (0.2)
Angina pectoris	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Palpitations	0.216	0	2 (0.4)	0	0	0	2 (0.1)
Ventricular tachycardia	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Ear and labyrinth disorders	0.727	0	1 (0.2)	1 (0.4)	1 (0.5)	1 (0.2)	4 (0.2)
Tinnitus	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Vertigo	0.439	0	1 (0.2)	1 (0.4)	1 (0.5)	0	3 (0.2)
Endocrine disorders	0.388	0	1 (0.2)	0	1 (0.5)	0	2 (0.1)
Autoimmune thyroiditis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Hypothyroidism	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Eye disorders	0.912	1 (0.2)	1 (0.2)	1 (0.4)	0	1 (0.2)	4 (0.2)
Corneal lesion	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Eye irritation	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Maculopathy	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Vitreous detachment	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Vitreous floaters	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	0.228	8 (1.8)	7 (1.5)	2 (0.9)	1 (0.5)	2 (0.4)	20 (1.1)
Abdominal distension	0.467	1 (0.2)	2 (0.4)	0	0	0	3 (0.2)
Abdominal pain	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Abdominal pain lower	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Abdominal pain upper	0.733	1 (0.2)	0	0	0	1 (0.2)	2 (0.1)
Constipation	0.007**	0	0	2 (0.9)	0	0	2 (0.1)
Diarrhea	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Dyspepsia	0.401	2 (0.4)	2 (0.4)	0	0	0	4 (0.2)
Gastritis	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Nausea	0.178	3 (0.7)	0	0	0	1 (0.2)	4 (0.2)
General disorders and administration site conditions	0.824	2 (0.4)	3 (0.6)	1 (0.4)	0	3 (0.6)	9 (0.5)
Asthenia	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Device malfunction	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Fatigue	0.534	1 (0.2)	0	0	0	0	1 (0.1)

Table 30. Number (%) of Subjects Reporting MedDRA Adverse Events Resulting in Withdrawal From the Study for the Subjects

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Generalized oedema	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Hunger	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Irritability	0.756	0	1 (0.2)	0	0	1 (0.2)	2 (0.1)
Malaise	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Oedema peripheral	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Infections and infestations	0.267	2 (0.4)	0	1 (0.4)	0	0	3 (0.2)
Influenza	0.395	1 (0.2)	0	1 (0.4)	0	0	2 (0.1)
Oral candidiasis	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Injury, poisoning and procedural complications	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Clavicle fracture	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Head injury	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Investigations	0.205	6 (1.3)	7 (1.5)	0	2 (0.9)	2 (0.4)	17 (0.9)
Alanine aminotransferase increased	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Aspartate aminotransferase increased	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Blood pressure systolic increased	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Blood urea increased	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Gamma-glutamyltransferase increased	0.179	2 (0.4)	0	0	0	0	2 (0.1)
Hepatic enzyme increased	0.388	0	1 (0.2)	0	1 (0.5)	0	2 (0.1)
Liver function test abnormal	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Weight increased	0.837	2 (0.4)	3 (0.6)	0	1 (0.5)	2 (0.4)	8 (0.4)
Musculoskeletal and connective tissue disorders	0.815	2 (0.4)	3 (0.6)	2 (0.9)	1 (0.5)	5 (1.1)	13 (0.7)
Arthralgia	0.216	0	0	0	0	2 (0.4)	2 (0.1)
Back pain	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Muscle spasms	0.741	2 (0.4)	2 (0.4)	2 (0.9)	0	2 (0.4)	8 (0.4)
Musculoskeletal pain	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Pain in extremity	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Sensation of heaviness	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.956	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.5)	1 (0.2)	5 (0.3)
Benign fallopian tube neoplasm	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Colon cancer stage IV	0.117	0	0	0	1 (0.5)	0	1 (0.1)

Table 30. Number (%) of Subjects Reporting MedDRA Adverse Events Resulting in Withdrawal From the Study for the Subjects

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Hodgkin's disease	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Malignant melanoma	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Uterine leiomyoma	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Nervous system disorders	0.381	1 (0.2)	7 (1.5)	2 (0.9)	2 (0.9)	4 (0.8)	16 (0.9)
Amnesia	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Balance disorder	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Cerebrovascular accident	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Disturbance in attention	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Dizziness	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Dysarthria	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Headache	0.275	0	3 (0.6)	0	0	2 (0.4)	5 (0.3)
Migraine	0.216	0	0	0	0	2 (0.4)	2 (0.1)
Migraine with aura	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Multiple sclerosis relapse	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Occipital neuralgia	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Tension headache	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Tremor	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Visual field defect	0.135	0	0	1 (0.4)	0	0	1 (0.1)
Psychiatric disorders	0.951	4 (0.9)	5 (1.1)	1 (0.4)	2 (0.9)	4 (0.8)	16 (0.9)
Anxiety	0.659	2 (0.4)	1 (0.2)	1 (0.4)	2 (0.9)	1 (0.2)	7 (0.4)
Depression	0.754	1 (0.2)	2 (0.4)	0	0	1 (0.2)	4 (0.2)
Dysphemia	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Insomnia	0.914	1 (0.2)	1 (0.2)	0	0	1 (0.2)	3 (0.2)
Mood altered	0.480	0	2 (0.4)	0	0	1 (0.2)	3 (0.2)
Suicidal ideation	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Reproductive system and breast disorders	<0.001***	2 (0.4)	4 (0.8)	2 (0.9)	15 (6.8)	8 (1.7)	31 (1.7)
Breast pain	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Breast tenderness	0.006**	0	1 (0.2)	1 (0.4)	4 (1.8)	1 (0.2)	7 (0.4)
Coital bleeding	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Dyspareunia	0.756	0	1 (0.2)	0	0	1 (0.2)	2 (0.1)
Menopausal symptoms	0.135	0	0	1 (0.4)	0	0	1 (0.1)

Table 30. Number (%) of Subjects Reporting MedDRA Adverse Events Resulting in Withdrawal From the Study for the Subjects

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843
Metrorrhagia	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Pelvic pain	<0.001***	0	0	0	3 (1.4)	0	3 (0.2)
Postmenopausal hemorrhage	0.388	0	1 (0.2)	0	1 (0.5)	0	2 (0.1)
Uterine hemorrhage	0.118	0	0	1 (0.4)	2 (0.9)	1 (0.2)	4 (0.2)
Uterovaginal prolapse	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Vaginal discharge	0.216	0	0	0	0	2 (0.4)	2 (0.1)
Vaginal hemorrhage	<0.001***	1 (0.2)	0	0	5 (2.3)	1 (0.2)	7 (0.4)
Vulvovaginal dryness	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Vulvovaginal pruritus	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0.289	0	0	0	1 (0.5)	2 (0.4)	3 (0.2)
Cough	0.216	0	0	0	0	2 (0.4)	2 (0.1)
Rhinitis allergic	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Skin and subcutaneous tissue disorders	0.753	3 (0.7)	2 (0.4)	2 (0.9)	3 (1.4)	4 (0.8)	14 (0.8)
Acne	0.576	0	0	0	0	1 (0.2)	1 (0.1)
Alopecia	0.554	1 (0.2)	0	0	1 (0.5)	2 (0.4)	4 (0.2)
Night sweats	0.716	1 (0.2)	0	1 (0.4)	1 (0.5)	1 (0.2)	4 (0.2)
Pruritus	0.733	1 (0.2)	1 (0.2)	0	0	0	2 (0.1)
Rash macular	0.576	0	1 (0.2)	0	0	0	1 (0.1)
Urticaria	0.185	0	0	1 (0.4)	1 (0.5)	0	2 (0.1)
Vascular disorders	0.217	9 (2.0)	4 (0.8)	3 (1.3)	3 (1.4)	2 (0.4)	21 (1.1)
Deep vein thrombosis	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Hot flush	0.244	6 (1.3)	3 (0.6)	3 (1.3)	0	2 (0.4)	14 (0.8)
Hypertension	0.371	1 (0.2)	0	0	1 (0.5)	0	2 (0.1)
Hypertensive emergency	0.117	0	0	0	1 (0.5)	0	1 (0.1)
Peripheral vascular disorder	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Phlebitis superficial	0.534	1 (0.2)	0	0	0	0	1 (0.1)
Phlebolith	0.576	0	1 (0.2)	0	0	0	1 (0.1)

Table 30. Number (%) of Subjects Reporting MedDRA Adverse Events Resulting in Withdrawal From the Study for the Subjects

System Organ Class[a] Preferred Term	Overall p-Value	Treatment					
		BZA 20 mg/ CE 0.45 mg n=445	BZA 20 mg/ CE 0.625 mg n=474	BZA 20 mg n=230	CE 0.45 mg/ MPA 1.5 mg n=220	Placebo n=474	Total n=1843

Classifications of adverse events are based on the MedDRA.
Overall p-value: refers to number of subjects data. p-Value for Chi-Square.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
BZA = bazedoxifene; CE = conjugated estrogens; MedDRA = Medical Dictionary for Regulatory Activities; MPA = medroxyprogesterone acetate; n = number of subjects in a treatment group.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

Deaths: One (1) subject died during the study. The subject, who had a history of tobacco use, and was randomized to placebo treatment, died 36 days after the last dose of test article due to arteriosclerosis of the coronary artery. The AE was not related to test article.

Vital Signs, Body Weight and ECGs: No significant differences were observed among the treatment groups in the number and percentage of subjects with blood pressure and body weight results that met the criteria for potential clinical importance (p=0.213). A total of 3 subjects (0.7%) in the BZA 20 mg/CE 0.625 mg treatment group had potentially clinically important changes in ECG results compared with 2 subjects (1.0%) in the BZA 20 mg group and 3 subjects (0.8%) in the placebo group. Overall, no significant differences across groups were observed in the number and percentage of subjects with ECG values meeting the criteria for potential clinical importance (p=0.328).

CONCLUSIONS:

The results for the primary variables showed that both doses of BZA/CE were safe to the endometrium while preventing bone loss in early postmenopausal women. Women treated with either dose of BZA/CE showed increases in BMD as compared with a decrease in BMD observed in women assigned to placebo treatment. The clinical effect was similar among all active treatment groups. These results also proved to be robust through various secondary analyses and analysis of biochemical markers of bone turnover in serum.

With a total exposure to BZA/CE (either dose combination) of 797 person years, no new safety signal was identified. BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were safe, with no new and unexpected safety findings during the 12 months of therapy. In this study, there is no evidence that BZA/CE was associated with a risk to the endometrium, to breast tissue and of thromboembolic or cardiac events compared with placebo. Laboratory test values, vital sign measurements, and ECG results did not suggest any new safety concerns during the 12 months of the study.

The incidence of endometrial hyperplasia after 1 year of therapy was <1% in both the BZA/CE treatment groups (BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg) in early postmenopausal women. The upper limits of 1-sided 95% CIs for the observed incidence of hyperplasia in both BZA/CE treatment groups were <4%. Both BZA/CE doses were shown to be safe in terms of protecting the endometrium.

In a subpopulation of early postmenopausal women with a Baseline T-score >-2.5, after 1 year of therapy, both BZA/CE treatment groups showed a significant increase in lumbar spine and total hip BMD compared with decreases observed in the placebo group.

For both BZA/CE treatment groups, increases in BMD were accompanied by a significant decrease in BTMs (osteocalcin, C-telopeptide, and P1NP) at Month 6 and Month 12 compared to placebo, consistent with a pattern indicating a decrease in bone turnover in these groups. Bone loss was significantly lower for both BZA/CE treatment groups than that for the placebo group for degrees of bone loss of >1% through >4%.

The cumulative rate of amenorrhea was similar to placebo in both the BZA/CE treatment groups over a 1 year treatment period. The bleeding and spotting profile of both BZA/CE

treatment groups was significantly better than that for the CE 0.45 mg/MPA 1.5 mg treatment group.

Significantly more subjects in the CE 0.45 mg/MPA 1.5 mg treatment group reported at least 1 day of breast tenderness compared to both BZA/CE or placebo treatment groups.

Both BZA/CE doses had a similar effect on BD as placebo. After 1 year of treatment, both doses of BZA/CE showed non-inferiority compared to placebo with regards to changes in mammographic breast density in a sub-population of postmenopausal women.

After 1 year of treatment, subjects in the BZA 20 mg/CE 0.625 mg treatment group showed significantly better responses to most sleep-related parameters as compared with the placebo treatment group. Subjects treated with BZA 20 mg/CE 0.625 mg fell asleep faster, and reported less sleep disturbances or sleep-related problems. Subjects treated with BZA 20 mg/CE 0.45 mg only reported less sleep disturbance and a faster time to sleep than placebo-treated subjects.

Daily doses of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were safe with no unexpected safety findings. No unexpected findings were observed during the study for changes in clinical laboratory or vital sign values.

In summary, the results from this study provide reassurance about endometrial safety of BZA/CE use in a population of early postmenopausal women while preventing bone loss without affecting breast density.