Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile

Rogerio A. Lobo, M.D.,[a] *JoAnn V. Pinkerton, M.D.,*[b] *Margery L. S. Gass, M.D.,*[c] *Maxine H. Dorin, M.D.,*[d] *Sheila Ronkin, M.D.,*[e] *James H. Pickar, M.D.,*[e] *and Ginger Constantine, M.D.*[e,*]

[a] Columbia University Medical Center, New York, New York; [b] University of Virginia Health System, Charlottesville, Virginia; [c] University of Cincinnati College of Medicine, Cincinnati, Ohio; [d] University of New Mexico Medical School, Albuquerque, New Mexico; and [e] Wyeth Research, Collegeville, Pennsylvania

Objective: To evaluate the effects of a tissue-selective estrogen complex (TSEC) composed of bazedoxifene/conjugated estrogens (BZA/CE) on menopausal symptoms, metabolic parameters, and overall safety.
Design: Multicenter, double-blind, placebo- and active-controlled phase 3 trial (Selective estrogens, Menopause, And Response to Therapy [SMART]-1).
Setting: Outpatient clinical.
Patient(s): Healthy, postmenopausal women (n = 3,397) age 40 to 75 with an intact uterus.
Intervention(s): Single tablets of BZA (10, 20, or 40 mg), each with CE (0.625 or 0.45 mg); raloxifene 60 mg; or placebo taken daily for 2 years.
Main Outcome Measure(s): Hot flushes, breast pain, vaginal atrophy, metabolic parameters, and adverse events.
Result(s): BZA (20 mg)/CE (0.625 or 0.45 mg) significantly reduced the frequency and severity of hot flushes and improved measures of vaginal atrophy compared with placebo. At week 12, the daily number of hot flushes decreased by 51.7% to 85.7% with all BZA/CE doses vs. 17.1% for placebo. BZA/CE improved lipid parameters and homocysteine levels, did not significantly change carbohydrate metabolism, and had only minor effects on some coagulation parameters. The incidences of breast pain and adverse events were similar between BZA/CE and placebo.
Conclusion: The TSEC composed of BZA (20 mg)/CE (0.625 or 0.45 mg) is an effective and safe treatment for menopausal symptoms. (Fertil Steril® 2009;92:1025–38. ©2009 by American Society for Reproductive Medicine.)

Key Words: Bazedoxifene, breast pain, coagulation, conjugated estrogens, hot flushes, metabolism, vaginal atrophy

An increasing number of women in the United States are postmenopausal. According to the U.S. Census Bureau, an estimated 60 million women will be over 45 years of age by the year 2010 (1). Because of the decreasing levels of estrogen associated with menopause, many women might experience bothersome symptoms, with the hallmark feature being vasomotor symptoms or hot flushes. Recent analyses of the risks and benefits of hormone therapy concluded that it is an appropriate option for such symptomatic women (2). Another significant concern for postmenopausal women is the risk of developing osteoporosis, with an estimated 8 million women affected and another 34 million women at risk (3).

Selective estrogen receptor modulators (SERMs) have been developed to treat postmenopausal osteoporosis. As a class, SERMs generally provide estrogen agonistic effects on bone and the liver, but may be agonistic or antagonistic for the uterus and vagina, and are usually antagonistic for the breast and brain, thus potentially inducing or worsening hot flushes in some women. An indole-based SERM, bazedoxifene (BZA), has been shown to be effective for the prevention and treatment of osteoporosis (4, 5) and to provide antagonistic effects on the breast and uterus (6–9).

In light of continued efforts to provide women with additional therapeutic options for the treatment of menopausal symptoms, consideration has been given to the pairing of BZA with estrogens in the form of a tissue-selective estrogen complex (TSEC). The partnering of BZA with conjugated estrogens might offer advantages over the use of progestins in women with an intact uterus receiving hormone therapy, including an improved safety and tolerability profile. The BZA/conjugated estrogens (CEs) combination has the potential to not only reduce vasomotor symptoms and prevent osteoporosis, but also to minimize or antagonize stimulatory effects on the breast and uterus, which may reduce breast tenderness (10) and decrease the occurrence of vaginal bleeding. The results of a preliminary phase 2 study (11) evaluating a TSEC at varying doses of BZA

Received October 20, 2008; revised February 11, 2009; accepted March 17, 2009; published online July 26, 2009.
* Clinical Investigators and sites listed in appendix.
Supported by Wyeth Research, Collegeville, Pennsylvania.
R.A.L. is a clinical trial investigator for Wyeth and is a consultant for Bayer, Schering, Plough-Organon, and Wyeth. J.V.P. is a consultant for Merck, Duramed, Novo Nordisk, and Wyeth, is a board member for Boehringer Ingelheim, National Women's Health Resource, and National American Menopause Society, is a multicenter trial PI for Solvay. M.L.S.G. received research grants from Boehringer-Ingelheim, Proctor & Gamble, and Wyeth and is a consultant for Proctor & Gamble, Wyeth, Eli Lilly, Palatin Technologies, Roche, Sciele, and Upsher-Smith Laboratories. M.H.D. is a speaker for Wyeth. S.R. is an employee of Wyeth Research. J.H.P. is an employee of Wyeth Research. G.C. is an employee of Wyeth Research.
Clinical trial registration information is available at http://www.ClinicalTrials.gov, NCT00675688.
Reprint requests: Rogerio A. Lobo, M.D., Department of Obstetrics and Gynecology, Columbia University Medical Center, 622 W. 168th St., PH-16, New York, NY 10032 (TEL: 646-756-8282; FAX: 646-756-8280; E-mail: ral35@columbia.edu).

Copyright ©2009 American Society for Reproductive Medicine, Published by Elsevier Inc.

(5–20 mg) with CEs (0.3 or 0.625 mg) indicated that doses of CE higher than 0.3 mg were necessary to consistently reduce the occurrence of hot flushes when combined with BZA at doses that prevented estrogen-induced endometrial proliferation.

This article reports findings from the Selective estrogens, Menopause, And Response to Therapy-1 (SMART-1) trial, a 2-year, randomized, double-blind, placebo- and active-controlled clinical trial evaluating the efficacy and safety of varying doses of BZA/CE in postmenopausal women. This report describes the effects of BZA/CE on menopausal symptoms (hot flushes, vaginal atrophy), metabolic parameters, as well as its overall safety profile. The effects of BZA/CE on endometrium, bone mineral density (BMD), and uterine bleeding are reported separately in this journal issue (12–14).

MATERIALS AND METHODS

Study Design

Healthy women (40–75 years of age) who were postmenopausal for at least 1 year were eligible for participation in this 2-year, double-blind, randomized, multicenter, placebo- and active–controlled phase 3 trial conducted at 94 study sites worldwide. All subjects were required to have an intact uterus and acceptable endometrial biopsy results at screening.

A subset of women was enrolled in the Osteoporosis Prevention I Substudy or the Osteoporosis Prevention II and Metabolic Substudy. The two osteoporosis substudies were designed to assess BMD changes in later and earlier postmenopausal women. Subjects in the Osteoporosis Prevention I Substudy were >5 years postmenopause, with a BMD T-score between −1 and −2.5 at the lumbar spine or total hip and at least one additional risk factor for osteoporosis (family history of osteoporosis, early menopause, current history of smoking, past history of excessive alcohol use, diet low in calcium, inactive lifestyle, thin and/or small frame, Caucasian or Asian). Subjects in the Osteoporosis Prevention II and Metabolic Substudy were ≥1 year but ≤5 years postmenopause with at least 1 risk factor for osteoporosis.

Treatments

Subjects were randomly assigned through a computerized randomization/enrollment interactive voice recognition system to one of eight treatment regimens, including six BZA/CE doses (BZA [10, 20, or 40 mg] each with CE [0.45 or 0.625 mg]), raloxifene 60 mg, or placebo. Subjects were required to take one capsule orally at approximately the same time each day and maintain a consistent daily intake of dietary and supplemental calcium and vitamin D (total daily calcium intake, 1,000–1,600 mg; vitamin D, 200–400 IU).

Use of the following concomitant medications was permitted: acetaminophen; inhaled steroids (maximum daily intake, 1,000 μg); dermal steroids; intra-articular injections (maximum of three injections during the treatment period); oral corticoids at standard therapeutic doses for periods of up to 10 days; up to two antihypertensive medications; and vitamin/mineral supplements if they had been taken continuously for ≥12 weeks before the study. Prohibited therapy included estrogen-, progestin-, androgen-, or SERM-containing medications other than the study drug. Also prohibited was the continued use of medications that could affect bone metabolism (osteoporosis substudies) or prescription lipid–lowering agents and anticoagulants other than aspirin (metabolic substudy).

Assessments

Subjects were instructed to record in daily diaries information on hot flushes, sexual activity/dyspareunia, and breast pain. Vaginal atrophy was measured by vaginal smears at months 6, 12, 18, and 24, which quantified the degree of maturation of the vaginal epithelium by the proportion of parabasal, intermediate, and superficial cells obtained in the sample.

Safety assessments included adverse event (AE) reporting and clinical laboratory evaluations (e.g., hematology, blood chemistry), which were performed at the screening visit and at months 3, 6, 12, 18, and 24. Reports of AEs were summarized using terms from the *Medical Dictionary for Regulatory Activities*. In the metabolic substudy, fasting serum samples were collected at randomization and at months 6, 12, and 18 to evaluate insulin and glucose levels. Coagulation factors (prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III activity, protein C activity, protein S activity, plasminogen activity, plasminogen activator inhibitor-1 [PAI-1] activity, PAI-1 antigen, and D–dimer) and lipid parameters (total cholesterol, high-density lipoprotein [HDL] cholesterol, low–density lipoprotein [LDL] cholesterol, very-low-density lipoprotein [VLDL] cholesterol, triglycerides, VLDL triglycerides, HDL_2 cholesterol, HDL_3 cholesterol, apoliprotein A1, apolipoprotein B, and lipoprotein [a]) were assessed in the metabolic substudy. Safety and metabolic data for month 24 (study end) are presented here.

Statistical Analyses

Analyses of any data of interest included only those subjects who received at least one dose of the study drug, in addition to criteria specific for the parameter of interest. Hot flush data were analyzed for the efficacy evaluable 1 population or those subjects who reported at least seven moderate or severe hot flushes per day or 50 per week during screening (n = 216). Complete data were summarized for the baseline week, for each week during weeks 1–12 (using a last observation carried forward approach), and for every four-week period thereafter. The mean daily number of hot flushes was calculated using only moderate and severe hot flushes, whereas the mean daily severity of hot flushes was calculated using all three intensities (1 = mild; 2 = moderate; and 3 = severe). Pairwise comparisons vs. placebo were made using an analysis of covariance (ANCOVA).

Vaginal epithelial maturation data were analyzed for the vulvar/vaginal atrophy population, or for those subjects with no more than 5% superficial cells at screening and those who had a baseline and at least one on-therapy assessment (n = 1,867). Vaginal atrophy was measured by the change from baseline in the percentage of superficial, intermediate, and parabasal cells at each time point using an ANCOVA, with treatment and center as factors and baseline value as covariate. The proportion of each cell type was analyzed using a nonparametric one-way Kruskal-Wallis test for between-group comparisons (vs. placebo) and a signed-rank test for within-group comparisons.

The incidence of sexual activity and dyspareunia was summarized for seven consecutive baseline days before treatment initiation and for sequential 28-day periods during the study. Breast pain data were analyzed for subjects with diary data for at least 5 of the 7 days during screening and at least 20 days for the relevant 4-week interval. Among-group differences in the incidence of breast pain during each time period (weeks 1–4, 5–8, and 9–12) were evaluated using Fisher's exact test. The mean change from baseline in the percentage of days with breast pain in a given 4-week interval was evaluated using ANCOVA, and pairwise comparisons versus placebo were made using the *t* test.

Data from the metabolic substudy were analyzed in those subjects who had baseline and on–therapy values for the parameter of interest. For lipid parameters, differences in the mean percent change from baseline at each time point between each BZA/CE treatment group and placebo were evaluated using an analysis of variance (ANOVA) model. For all other parameters (e.g., coagulation, carbohydrate), the mean absolute change from baseline at each time point was assessed; within- and between-group comparisons (vs. placebo) were made using the ANOVA model.

Among-group differences in the incidence of AEs were evaluated using χ^2 analysis (overall *P* value), and Fisher's exact test was used to compare the incidence of AEs between each BZA/CE group and the placebo group. For each laboratory parameter, the adjusted mean change from baseline as well as the number and percentage of subjects with potentially clinically important (PCI) values were summarized. Within- and among-group differences in the mean change from baseline for all laboratory tests were evaluated using ANCOVA. Pairwise comparisons for the incidence of PCI values were made using Fisher's exact test.

RESULTS

Subjects

A total of 3,397 subjects were randomly assigned to a treatment group and received at least 1 dose of the study drug (Fig. 1). Subject demographics and baseline characteristics were similar across all treatment groups (Table 1). The rates of study discontinuation were not significantly different among treatment groups (range,

29.8–35.7%; Fig.1). The most frequent reason for discontinuation was AEs, followed by subject request unrelated to the study. A significantly higher percentage of subjects in the placebo group withdrew from the study because of unsatisfactory response compared with those in any other treatment group ($P = 0.002$).

Hot Flushes

Examination of the mean daily number of moderate and severe hot flushes demonstrated that all doses of BZA/CE provided significantly better relief of hot flushes than placebo at most time points ($P < 0.01$; Fig. 2A). At week 12, the adjusted mean change from baseline in the average daily number of hot flushes for the BZA/CE treatment groups ranged from −5.53 to −8.98 (−51.7% to −85.7%) compared with −2.45 (−17.1%) and −5.29 (−44.1%) for the placebo and raloxifene treatment groups, respectively. Treatment with BZA (20 mg)/CE (0.625 or 0.45 mg) was significantly more effective than placebo at every weekly time point from weeks 6 to 12. Improvements in the frequency and severity of hot flushes observed with BZA (10 or 20 mg)/CE (0.625 or 0.45 mg) were sustained through the second year of therapy (data not shown). Although the daily number of hot flushes reported with BZA (40 mg)/CE (0.625 mg) or BZA (40 mg)/CE (0.45 mg) was also significantly reduced compared with placebo at week 12, this decrease was not as great as that noted with BZA (10 or 20 mg)/CE (0.625 or 0.45 mg) at most time points (Fig. 2). Bazedoxifene/CE groups demonstrated significant decreases in hot flush number and severity compared with raloxifene; significant differences in number and/or severity were seen as early as week 2 for BZA (10 mg)/CE (0.625 or 0.45 mg) and at week 6 for BZA (20 mg)/CE (0.625 or 0.45 mg), and continued through week 12.

Vaginal Atrophy

Treatment with BZA (10 mg)/CE (0.625 mg or 0.45 mg) and BZA (20 mg)/CE (0.625 or 0.45 mg) was significantly more effective than placebo in increasing the mean proportion of superficial cells from baseline to most time points ($P < 0.001$; Fig. 3A). Furthermore, all four BZA/CE doses containing BZA (10 or 20 mg)/CE (0.625 or 0.45 mg) were significantly more effective than placebo in increasing the mean proportion of intermediate cells and decreasing the proportion of parabasal cells from baseline to all time points ($P < 0.001$; Fig. 3B, C). There was a dose–related attenuation of the beneficial estrogenic effect on vaginal atrophy with increasing doses of BZA, which was most noted with BZA (40 mg)/CE (0.625 or 0.45 mg). However, with BZA doses of 10 and 20 mg, the effects on vaginal endpoints were substantially improved compared with raloxifene or placebo.

Sexual Activity, Dyspareunia, and Breast Pain

At baseline, sexual activity was reported by 34–43% of the participants and dyspareunia was reported by 16–26%. There were no significant among-group differences in the incidence of sexual activity throughout the study. Compared with subjects who received placebo or raloxifene, subjects treated with BZA (10 mg)/CE (0.625 mg) had a lower incidence of dyspareunia at weeks 5–8 ($P < 0.05$). With BZA (10 mg)/CE (0.625 mg) and BZA (20 mg)/CE (0.625 or 0.45 mg) there was a significantly lower incidence of dyspareunia during weeks 9–12 ($P < 0.05$).

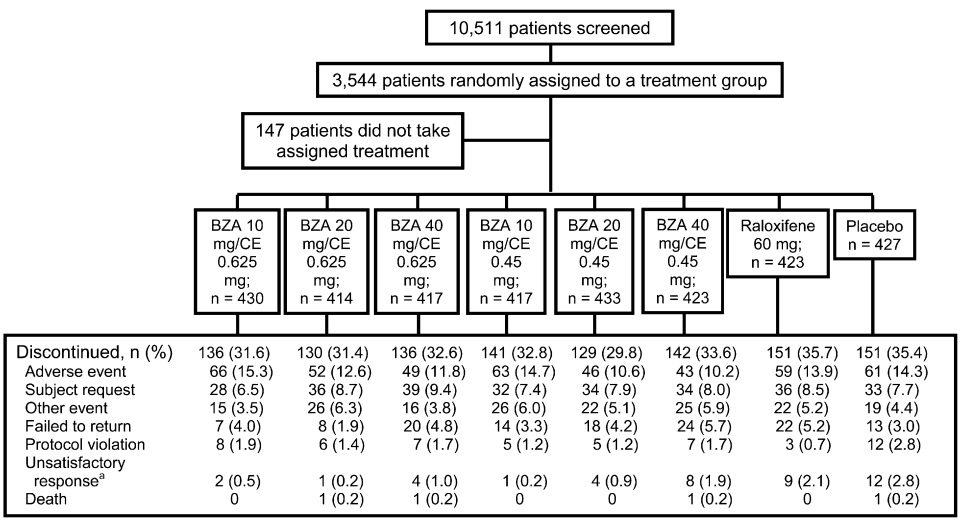
For most of the weeks analyzed, BZA (10 and 20 mg)/CE (0.625 or 0.45 mg) had significantly less dyspareunia than with raloxifene $P < 0.05$. Breast pain occurred with similar frequency for subjects in the BZA/CE, raloxifene, and placebo groups, and there were no significant differences in the incidence of breast pain among the groups for any 28-day interval.

Metabolic Parameters

The adjusted mean percent changes from baseline in LDL and HDL cholesterol are presented in Figure 4. Reductions in LDL cholesterol for all BZA/CE doses (range,−5.7% to −10.9%) were significantly

FIGURE 1

Disposition of study subjects. Following screening, a total of 3,544 subjects were randomly assigned to 1 of 8 treatment groups, and 3,397 subjects took at least one dose of the study drug. The diagram outlines reasons for study discontinuation for each treatment group. *Note:* BZA = bazedoxifene; CE = conjugated estrogens. [a]Overall $P < 0.01$; χ^2 analysis.



Discontinued, n (%)	136 (31.6)	130 (31.4)	136 (32.6)	141 (32.8)	129 (29.8)	142 (33.6)	151 (35.7)	151 (35.4)
Adverse event	66 (15.3)	52 (12.6)	49 (11.8)	63 (14.7)	46 (10.6)	43 (10.2)	59 (13.9)	61 (14.3)
Subject request	28 (6.5)	36 (8.7)	39 (9.4)	32 (7.4)	34 (7.9)	34 (8.0)	36 (8.5)	33 (7.7)
Other event	15 (3.5)	26 (6.3)	16 (3.8)	26 (6.0)	22 (5.1)	25 (5.9)	22 (5.2)	19 (4.4)
Failed to return	7 (4.0)	8 (1.9)	20 (4.8)	14 (3.3)	18 (4.2)	24 (5.7)	22 (5.2)	13 (3.0)
Protocol violation	8 (1.9)	6 (1.4)	7 (1.7)	5 (1.2)	5 (1.2)	7 (1.7)	3 (0.7)	12 (2.8)
Unsatisfactory response[a]	2 (0.5)	1 (0.2)	4 (1.0)	1 (0.2)	4 (0.9)	8 (1.9)	9 (2.1)	12 (2.8)
Death	0	1 (0.2)	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)

Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

TABLE 1

Subject demographic and baseline characteristics.

Characteristic	CE (0.625 mg) BZA (10 mg)	CE (0.625 mg) BZA (20 mg)	CE (0.625 mg) BZA (40 mg)	CE (0.45 mg) BZA (10 mg)	CE (0.45 mg) BZA (20 mg)	CE (0.45 mg) BZA (40 mg)	Raloxifene (60 mg)	Placebo
Age, y								
N	430	414	417	430	433	423	423	427
Mean (SD)	56.35 (5.60)	56.29 (5.98)	56.68 (5.81)	56.84 (5.73)	56.22 (5.80)	56.31 (5.76)	56.54 (5.72)	56.48 (6.04)
Ethnic origin								
White	354 (82.33)	343 (82.85)	341 (81.77)	346 (80.47)	351 (81.06)	327 (77.30)	341 (80.61)	340 (79.63)
Black	58 (13.49)	53 (12.80)	55 (13.19)	57 (13.26)	54 (12.47)	66 (15.60)	57 (13.48)	66 (15.46)
Hispanic	13 (3.02)	13 (3.14)	16 (3.84)	15 (3.49)	20 (4.62)	18 (4.26)	14 (3.31)	15 (3.51)
Other	5 (1.16)	5 (1.20)	5 (1.20)	12 (2.79)	8 (1.84)	12 (2.83)	11 (2.59)	6 (1.40)
BMI, kg/m^2								
N	430	412	417	430	433	423	423	426
Mean (SD)	25.74 (3.44)	25.87 (3.55)	25.66 (3.18)	25.83 (3.36)	25.97 (3.45)	25.57 (3.46)	25.92 (3.28)	25.94 (3.54)
Years since last menstrual period								
N	430	414	417	429	433	423	423	427
Mean (SD)	7.80 (5.65)	8.10 (5.71)	8.29 (5.71)	7.94 (5.60)	8.11 (5.70)	7.9 (5.80)	8.33 (5.83)	8.36 (5.78)

Note: BMI= body mass index.

Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

greater compared with placebo (range, −0.1 to 2.2%) at all time points ($P < 0.01$). Increases in HDL cholesterol for all BZA/CE doses (range, 7.0–13.5%) were significantly greater compared with placebo (range, 1.3% to 5.4%) at all time points ($P < 0.05$), and significantly greater compared with raloxifene (range, 3.1–6.6%) at most time points ($P < 0.05$). There was no apparent dose-related attenuation of HDL cholesterol levels with BZA, and the observed increases were sustained throughout 2 years of therapy.

Changes in other lipid parameters are provided in Table 2. Total cholesterol decreased from baseline for all BZA/CE treatment groups at all time points (range, −0.8 to −3.7%). At month 24, the increase from baseline in triglycerides was higher for all BZA/CE doses (range, 12.0–25.1%) compared with placebo (6.1%) or raloxifene (6.9%).

Increases from baseline in HDL_2 cholesterol noted for all BZA/CE treatment groups (range, 17.9–33.4% at month 24) were significantly greater compared with placebo at all time points and raloxifene at some time points ($P < 0.05$). There was a minor attenuation of the increase seen in HDL_2 cholesterol levels as the dose of BZA within the TSEC increased.

Significant increases from baseline in apolipoprotein A1 reported with BZA/CE (range, 9.0–11.2% at month 24) were not attenuated by increasing the BZA dose and were greater than that observed with raloxifene or placebo (Table 2). Decreases from baseline in apolipoprotein B levels were observed with BZA (20 or 40 mg)/CE (0.625 or 0.45 mg) at all time points (range, −0.7 to −2.0% at month 24), whereas increases were noted with placebo. Reductions in lipoprotein (a) levels noted for all BZA/CE treatment groups were significantly greater compared with the placebo group at months 12 and 24 ($P < 0.05$), and significantly greater compared with the raloxifene group at month 12 ($P \leq 0.05$).

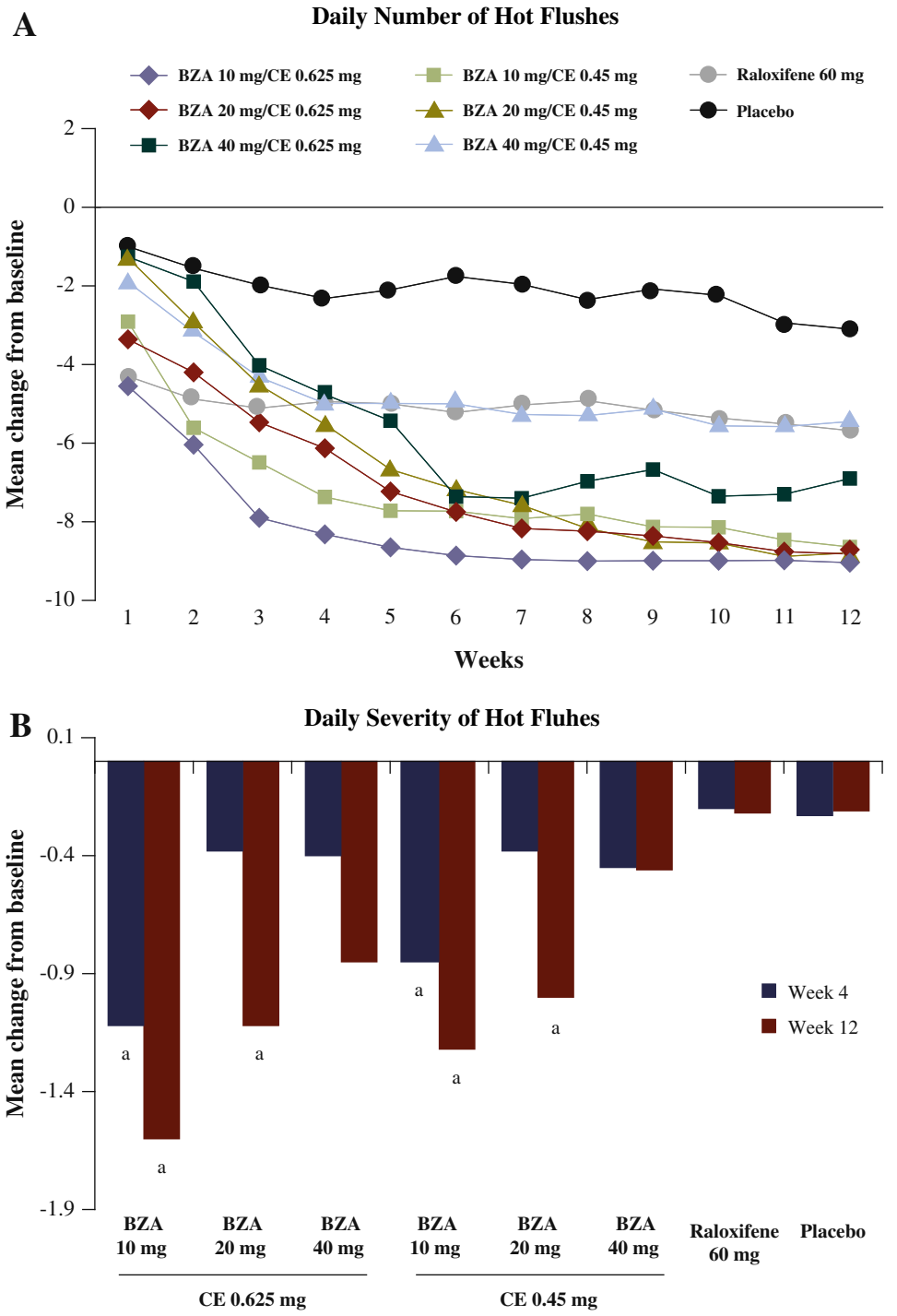
There were no significant changes in fasting glucose, fasting insulin, or C-reactive protein levels relative to baseline or placebo at any time point with BZA/CE. Decreases from baseline in plasma homocysteine were significant for the BZA/CE treatment groups at all time points ($P < 0.05$), with the exception of BZA (10 mg)/CE (0.625 mg) at months 18 and 24. Decreases in plasma homocysteine with BZA (40 mg)/CE (0.625 mg) and BZA (10 mg)/CE (0.45 mg) were significantly greater than that observed with placebo at all time points ($P < 0.05$).

None of the BZA/CE doses had any effect on partial thromboplastin time, prothrombin time, or serum concentrations of D-dimer. Effects of BZA/CE on fibrinolysis (assessed by plasminogen activity, PAI-1 activity, and serum levels of PAI-1 antigen) were similar to those with known beneficial effects of estrogen. All six doses of BZA/CE were associated with small decreases from baseline in mean PAI-1 activity (range, −1.3 to −3.1 IU/mL at month 24; $P < 0.05$ for BZA [10 and 20 mg]/CE [0.625 mg] and BZA [40 mg]/CE [0.45 mg]) and PAI-1 antigen levels (range, −0.92 to −6.6 mg/day at month 24; $P < 0.05$ for BZA [20 mg]/CE [0.625 mg]), and small increases from baseline in mean plasminogen activity (range, 0.07–0.11 mg/day at month 24; $P < 0.001$ for all BZA/CE doses). There were small decreases from baseline in mean levels of the procoagulation factor fibrinogen for all BZA/CE treatment groups (range, −0.3 to −0.5 mg/day), which were significantly different from those observed in the placebo group ($P < 0.001$). There was no significant change with raloxifene. (Note: Overall for these coagulation parameters, changes in the raloxifene group were similar to those seen with BZA/CE with no statistically significant difference between raloxifene 60 mg and either BZA/CE dose).

There was no significant change from baseline in protein C activity for any BZA/CE doses relative to placebo. However, some increases in protein C activity observed with BZA/CE were significantly different from the decreases observed with raloxifene at some time points ($P < 0.05$). With the exception of BZA (20 mg)/CE (0.45 mg) at month 6, all doses of BZA/CE were associated with small but significantly greater changes in protein S activity (range, −0.1 to 0.1 mg/day) compared with placebo at all time points ($P < 0.05$). At month 24, minor increases in protein S activity

FIGURE 2

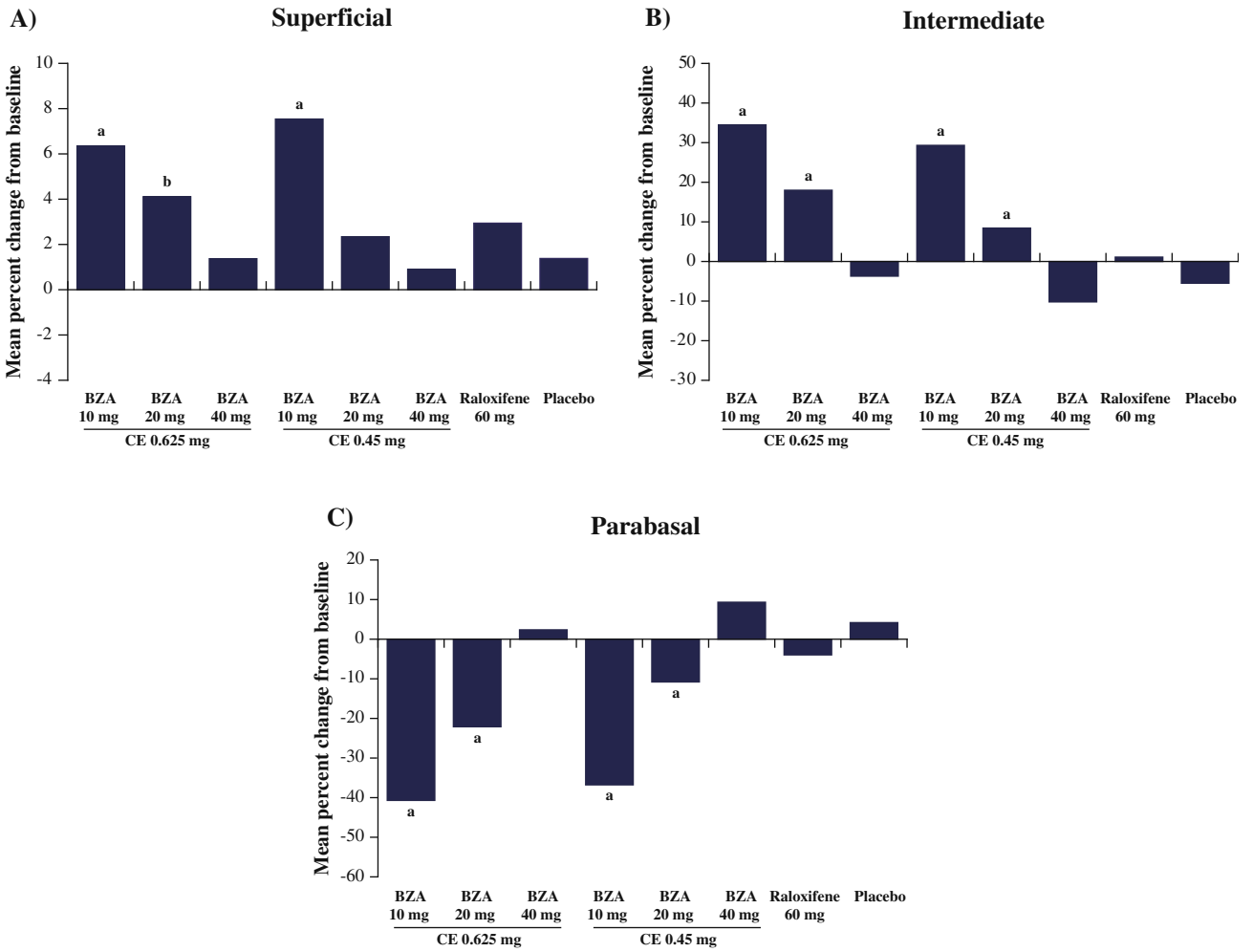
Mean changes from baseline in (**A**) the daily number and (**B**) the severity of hot flushes in each treatment group. (**A**) Mean change in the daily number of moderate or severe hot flushes for weeks 1–12. $P < 0.05$ for all BZA/CE doses compared with placebo for weeks 5–12. $P < 0.05$ for BZA (10 mg)/CE (0.625 mg) at all time points and for BZA (10 mg)/CE (0.45 mg) at all time points except Week 1. (**B**) Adjusted mean change in total hot flush severity (mild, moderate, and severe) from baseline at weeks 4 and 12. *Note:* BZA = bazedoxifene; CE = conjugated estrogens. [a]$P < 0.001$ vs. placebo.



Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

FIGURE 3

Adjusted mean percent changes from baseline in the proportion of superficial, intermediate, and parabasal cells at month 24. Vaginal atrophy was assessed by vaginal smears, which were obtained from those who took at least one dose of the study drug, had a baseline and at least one on-therapy value, and had no more than 5% superficial cells at screening. *Note:* BZA = bazedoxifene; CE = conjugated estrogens. [a]$P < 0.001$ vs. placebo. [b]$P < 0.01$ vs. placebo.



Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

were noted in all BZA/CE treatment groups, whereas decreases were observed at earlier time points. Changes in antithrombin III activity (range, −0.1 to −0.3 mg/day) were also small but significantly greater compared with placebo for all BZA/CE doses ($P < 0.05$), with the exception of BZA (20 mg)/CE (0.625 mg) at month 6. Changes from baseline in antithrombin III activity were similar for subjects who received raloxifene or BZA/CE. There were no appreciable dose-related effects of BZA/CE on anticoagulation factors.

Adverse Events

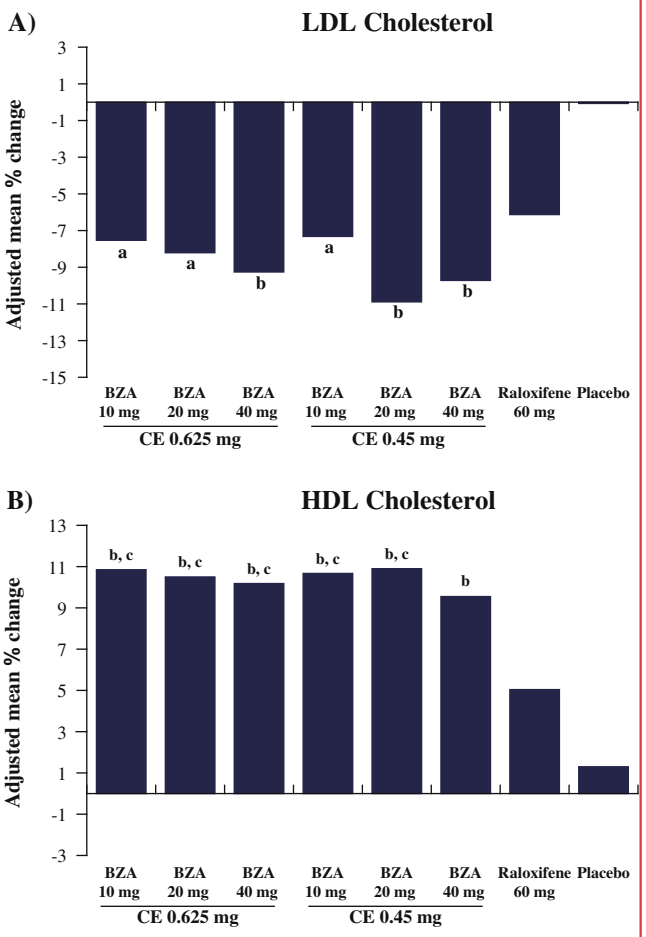
Overall, the incidence of AEs and serious AEs was similar among treatment groups (Table 3). There were no significant differences in the incidence of treatment-emergent AEs among groups (range, 90–94%; Table 3). The majority of treatment-emergent AEs, which were generally mild or moderate in severity, were not considered related to the study drug. There were no significant among-group differences in the incidence of these AEs. There were 6 deaths in the study, which were not thought to be study related. These deaths were caused by bronchoaspiration, intracerebral hemorrhage secondary to metastatic lung cancer, chronic obstructive airway disease, unknown causes, and accidental injury (two subjects).

Venous Thromboembolic Events

Overall, the incidence of venous thromboembolic events (VTEs) was similar for subjects treated with BZA/CE or placebo (0.76 vs. 1.56 per 1,000 women-years, respectively; relative risk, 0.48; 95% confidence interval [CI], 0.05–4.66). Two subjects in the BZA/CE treatment groups and one subject in the placebo group reported deep vein thrombosis. Pulmonary embolism was reported in one subject who received BZA (40 mg)/CE (0.625 mg). There were no reports of retinal vein thrombosis. Similarly, the incidence of superficial thromboses or phlebitis was low across all treatment groups (<1%), with no statistically significant among-group differences; importantly, none of these cases were classified as VTEs.

FIGURE 4

Adjusted mean percent changes from baseline in (**A**) LDL cholesterol and (**B**) HDL cholesterol levels in each treatment group (metabolic substudy) at month 24. The adjusted mean percent changes from baseline in levels of LDL cholesterol and HDL cholesterol were quantified for each treatment group. *Note:* BZA = bazedoxifene; CE = conjugated estrogens; HDL = high-density lipoprotein; LDL = low-density lipoprotein. [a]$P < 0.001$ vs. placebo. [b]$P < 0.01$ vs. placebo. [c]$P < 0.05$ vs. raloxifene.



Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

Cardiovascular AEs

The cardiovascular AEs of interest included myocardial infarction, coronary artery disease, and coronary artery insufficiency. The incidence of cardiovascular AEs was low (<1%) across all treatment groups, with no significant differences among groups. Compared with subjects who received placebo, the relative risk of experiencing a myocardial infarction with BZA/CE was 0.48 (95% CI, 0.05–4.66), or an incidence of 0.76 vs. 1.56 per 1,000 woman-years. For coronary artery disease and coronary artery insufficiency, the relative risk with BZA/CE vs. placebo was 1.29 (95% CI, 0.16–10.34), or an incidence of 2.02 vs. 1.56 per 1,000 women–years.

Clinical Laboratory Evaluations

The percentage of subjects with PCI increases in cholesterol levels at any time point was similar across all treatment groups. The incidence of PCI increases in cholesterol levels was 8.1% in the placebo group and 5.7% in the raloxifene group, and it did not exceed 6.5% in any BZA treatment group. However, significantly higher percentages of subjects in the BZA/CE treatment groups experienced PCI increases in triglyceride levels compared with the placebo group ($P < 0.05$). A total of five subjects treated with BZA/CE had triglyceride values that were considered clinically important. Analysis of other laboratory safety data for blood chemistry and hematology parameters demonstrated no trends of concern. Results of liver function tests also indicated no values of clinical importance.

Discussion

The TSEC was designed to provide tissue-selective activities of a SERM with the proven benefits of estrogen therapy (ET). The SMART-1 trial evaluated the efficacy and safety of the first TSEC composed of BZA/CE in postmenopausal women over a 2-year period. Findings from this study demonstrated favorable effects of BZA/CE on the relief of menopausal symptoms. Specifically, BZA (20 mg)/CE (0.625 or 0.45 mg) were significantly and clinically more effective than placebo in reducing the incidence of hot flushes, and BZA (20 mg)/CE (0.625 or 0.45 mg) also significantly reduced the severity of hot flushes compared with placebo. The BZA/CE groups decreased the daily number of hot flushes by 51.7–85.7% compared with only 17.1% with placebo. Whereas raloxifene has been shown to increase hot flushes in this population, in our study, raloxifene was associated with a numeric reduction in flush frequency, but not severity; however, BZA (10 and 20 mg)/CE groups BZA/CE groups reduced both hot flush frequency and severity significantly better than raloxifene. Furthermore, BZA (20 mg)/CE (0.625 or 0.45 mg) was significantly more effective than placebo in improving vaginal atrophy with significant increases in superficial and intermediate cells and reductions in parabasal cells. Accordingly, BZA (20 mg)/CE (0.625 or 0.45 mg) significantly reduced the incidence of dyspareunia relative to placebo. Breast pain is known to be increased in women taking estrogen/progestin therapy (EPT) (10). In this study, none of the BZA/CE doses increased the incidence of breast pain compared with placebo or raloxifene.

The menopausal transition is known to confer unfavorable changes in lipid and carbohydrate metabolism (15, 16), which may be associated with an increased risk of cardiovascular disease in women (17, 18). In this study, treatment with all BZA/CE regimens was associated with decreases in total cholesterol. Importantly, increases in LDL and decreases in HDL cholesterol are known risk factors for cardiovascular disease in women (19, 20). All BZA/CE doses were associated with marked decreases in LDL and increases in HDL cholesterol throughout the 2-year study period. Greater improvements in HDL cholesterol, HDL_2 cholesterol, and apolipoprotein A1 were observed with administration of BZA/CE compared with raloxifene. Such favorable effects on lipid parameters have previously been observed in studies that randomized women to receive ET or EPT for up to 3 years (21–23).

A minor attenuating effect on HDL cholesterol levels was noted with increasing dose of BZA. However, the reductions in LDL cholesterol and apolipoprotein B appeared to be even greater with increasing dose of BZA, particularly when paired with CE (0.45 mg). Decreases in PAI-1 activity and PAI-1 antigen levels were also observed with BZA/CE treatment. Improvements in lipoprotein (a) observed with BZA/CE treatment in this study are consistent with those observed with EPT in the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial (23) and the Heart and Estrogen/progestin Replacement Study

TABLE 2

Adjusted mean changes from baseline in selected lipid and coagulation parameters at month 24 (metabolic substudy).

Parameters	CE (0.625 mg)			CE (0.45 mg)			Raloxifene (60 mg)	Placebo
	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)	BZA (10 mg)	BZA (20 mg)	BZA (40 mg)		
Mean (SE) percent change								
Lipid parameters								
Total cholesterol	−2.3 (1.3)	−2.6 (1.4)	−2.3 (1.4)	−2.3 (1.4)	−3.7 (1.3)[a]	−3.4 (1.3)	−2.6 (1.4)	−0.2 (1.4)
Triglycerides	18.8 (4.9)	25.1 (5.1)[b,c]	23.6 (5.0)[a,d]	13.3 (5.3)	23.1 (4.7)[b,d]	12.0 (4.9)	6.9 (5.2)	6.1 (5.0)
HDL_2-C	33.4 (4.9)[c,e]	28.4 (5.1)[d,e]	17.9 (5.0)[b]	30.1 (5.3)[c,e]	28.2 (4.7)[d,e]	21.0 (4.9)[e]	10.7 (5.2)	−4.3 (5.0)
Apo A1	11.2 (1.3)[c,e]	11.1 (1.4)[c,e]	10.9 (1.4)[c,e]	9.4 (1.4)[e]	11.1 (1.3)[c,e]	9.0 (1.3)[e]	6.0 (1.4)	1.2 (1.4)
Apo B	1.4 (1.8)	−2.0 (1.9)[a]	−0.7 (1.9)	−0.7 (2.0)	−1.9 (1.7)[a]	−1.9 (1.8)[a]	−0.2 (1.9)	4.2 (1.9)
Lp(a)	−21.4 (3.0)[e]	−21.2 (3.1)[b]	−19.4 (3.1)[b]	−18.7 (3.2)[b]	−19.0 (2.8)[b]	−16.9 (3.0)[a]	−14.9 (3.2)	−7.7 (3.1)
Mean (SE) change, mg/day								
Coagulation factors								
Fibrinogen	−0.38 (0.07)[e]	−0.50 (0.07)[e]	−0.40 (0.07)[e]	−0.39 (0.07)[e]	−0.44 (0.06)[e]	−0.48 (0.07)[e]	−0.36 (0.07)	0.01 (0.07)
Protein C activity	0.06 (0.02)[d]	0.04 (0.02)[d]	0.02 (0.02)	0.04 (0.02)[d]	0.03 (0.01)	0.01 (0.02)	−0.01 (0.02)	0.03 (0.02)
Protein S activity	0.02 (0.02)[e,c]	0.07 (0.02)[b]	0.07 (0.02)[b]	0.07 (0.02)[b]	0.09 (0.02)[b]	0.08 (0.02)[b]	0.11 (0.02)	0.16 (0.02)
Antithrombin III activity	−0.29 (0.02)[b]	−0.28 (0.02)[b]	−0.28 (0.02)[b]	−0.27 (0.02)[a]	−0.27 (0.01)[a]	−0.28 (0.02)[b]	−0.26 (0.02)	−0.22 (0.02)

Note: Apo = apolipoprotein; HDL_2-C = high-density lipoprotein 2 cholesterol; Lp(a) = lipoprotein (a).

[a] $P < 0.05$ vs. placebo.
[b] $P < 0.01$ vs. placebo.
[c] $P < 0.01$ vs. raloxifene.
[d] $P < 0.05$ vs. raloxifene.
[e] $P < 0.001$ vs. placebo.

Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

TABLE 3

Summary of safety profile and incidence (≥10% in any treatment group) of treatment-emergent AEs.

	CE (0.625 mg)			CE (0.45 mg)				
	BZA (10 mg) n = 430	BZA (20 mg) n = 414	BZA (40 mg) n = 417	BZA (10 mg) n = 430	BZA (20 mg) n = 433	BZA (40 mg) n = 423	Raloxifene (60 mg) n = 423	Placebo n = 427
Any AE	403 (93.7)	382 (92.3)	384 (92.1)	400 (93.0)	401 (92.6)	381 (90.1)	391 (92.4)	392 (91.8)
Any serious AE	32 (7.24)	23 (5.6)	24 (5.8)	35 (8.1)	26 (6.0)	26 (6.1)	32 (7.6)	34 (8.0)
Any TEAE	403 (93.7)	382 (92.3)	384 (92.1)	400 (93.0)	401 (92.6)	381 (90.1)	391 (92.4)	392 (91.8)
Body as a whole								
Abdominal pain	56 (13.0)	39 (9.4)	38 (9.1)	41 (9.5)	54 (12.5)	38 (90.1)	36 (8.5)	32 (7.5)
Influenza	74 (17.2)	78 (18.8)	72 (17.3)	80 (18.6)	97 (22.4)	89 (21.0)	91 (21.5)	90 (21.1)
Headache	141 (32.8)	129 (31.2)	112 (26.9)	141 (32.8)	135 (31.2)	119 (28.1)	126 (29.8)	117 (27.4)
Infections and infestations	278 (64.7)	252 (60.9)	243 (58.3)	261 (60.7)	276 (63.7)	238 (56.3)	245 (57.9)	254 (59.5)
Digestive system								
Diarrhea	28 (6.5)	28 (6.8)	30 (7.2)	35 (8.1)	44 (10.2)	30 (7.1)	36 (8.5)	26 (6.1)
Abdominal pain upper	43 (10.0)	50 (12.1)	51 (12.2)	54 (12.6)	51 (11.8)	47 (11.1)	42 (9.9)	31 (7.3)
Nausea	30 (7.0)	30 (7.2)	31 (7.4)	32 (7.4)	46 (10.6)	29 (6.9)	27 (6.4)	23 (5.4)
Musculoskeletal system								
Arthralgia	98 (22.8)	110 (26.6)	97 (23.3)	104 (24.2)	101 (23.3)	119 (28.1)	122 (28.8)	112 (26.2)
Back pain	109 (25.3)	107 (25.8)	87 (20.9)	110 (25.6)	106 (24.5)	82 (19.4)	89 (21.0)	86 (20.1)
Muscle spasms[a]	44 (10.2)	30 (7.2)	45 (10.8)	40 (9.3)	47 (10.9)	41 (9.7)	35 (8.3)	22 (5.2)
Myalgia	58 (13.5)	61 (14.7)	55 (13.2)	56 (13.0)	53 (12.2)	51 (12.1)	60 (14.2)	58 (13.6)
Pain in extremity	53 (12.3)	60 (14.5)	61 (14.6)	73 (17.0)	70 (16.2)	58 (13.7)	59 (13.9)	63 (14.8)
Nervous system								
Insomnia	35 (8.1)	23 (5.6)	33 (7.9)	33 (7.7)	38 (8.8)	38 (9.0)	46 (10.9)	48 (11.2)
Respiratory system								
Nasopharyngitis	69 (16.0)	77 (18.6)	65 (15.6)	68 (15.8)	79 (18.2)	56 (13.2)	60 (14.2)	66 (15.5)
Sinusitis	37 (8.6)	43 (10.4)	36 (8.6)	38 (8.8)	27 (6.2)	21 (5.0)	36 (8.5)	41 (9.6)
Upper respiratory infection	54 (12.6)	42 (10.1)	36 (8.6)	47 (10.9)	52 (12.0)	47 (11.1)	55 (13.0)	47 (11.0)
Pharyngolaryngeal pain	43 (10.0)	40 (9.7)	37 (8.9)	33 (7.7)	48 (11.1)	36 (8.5)	46 (10.9)	37 (8.7)
Urogenital system								
Urinary tract infection	36 (8.4)	42 (10.1)	43 (10.3)	40 (9.3)	40 (9.2)	32 (7.6)	35 (8.3)	35 (8.2)

Note: TEAE = treatment-emergent adverse event.

[a] $P < 0.05$ overall.

Lobo. Effects of BZA/CE on menopausal symptoms. Fertil Steril 2009.

(HERS) (24). This beneficial effect on lipoprotein (a) observed with BZA/CE in the present study was greater than the response with placebo or raloxifene at month 12 and was further enhanced at month 24.

A favorable decrease in fibrinogen activity was noted with all BZA/CE doses, a finding supported by that reported with ET and EPT in the HOPE trial (23). Also consistent with findings of the HOPE trial were the changes in protein S activity and antithrombin III activity noted with BZA/CE vs. placebo. No significant changes in carbohydrate metabolism or serum concentrations of D-dimer were observed with any BZA/CE regimens throughout the study period. Because CE alone is known to reduce levels of fasting insulin, future studies will help determine whether BZA might affect this beneficial estrogen response. It is also important to note that any beneficial effects of BZA/CE on surrogate markers might not predict clinical events.

Overall, BZA/CE was generally well tolerated and demonstrated a safety profile similar to that of placebo. The incidence of AEs, serious AEs, and study discontinuations owing to AEs was similar across all treatment groups. Treatment with BZA/CE doses was not associated with an increased risk of VTEs or cardiovascular AEs; however, it is important to note that a longer period of observation in a larger population of subjects will be able to provide definitive risk information regarding possible adverse effects of therapy, as this study was not powered to detect small differences in these cardiovascular safety endpoints.

In this study, analysis of most clinical laboratory determinations (e.g., hematology, blood chemistry, liver function) revealed no clinically important differences among treatment groups and no trends of concern. In that the pairing of BZA and CE alleviates the need for a progestin, it is of interest to determine whether BZA attenuates any of the beneficial estrogenic effects of CE on metabolism. Among the parameters assessed in this study, the higher BZA dose (40 mg) was found to decrease, somewhat, the beneficial effect of CE on hot flushes and vaginal atrophy. Apart from a relatively minor attenuation noted for HDL_2 cholesterol, no other attenuating effects of BZA on clinical laboratory determinations were observed. For instance, triglycerides were unaffected by BZA dose, and some estrogenic effects were enhanced with increasing BZA dose, including decreases in LDL cholesterol.

One possible limitation of this study in evaluating the relief of vasomotor symptoms and vaginal atrophy is the wide range in ages of the subject population (45–70 years of age), because the occurrence of menopausal symptoms is typically highest in the early

years of menopause. However, an important objective of the SMART-1 trial was to assess the efficacy of BZA/CE for the prevention of postmenopausal osteoporosis, requiring a postmenopausal population at sufficient risk for osteoporosis and enrolling women of increasing age. Nevertheless, BZA/CE was associated with effective relief of menopausal symptoms in postmenopausal women of varying ages.

In conclusion, the SMART-1 trial showed that the administration of a TSEC that partners BZA and CE was effective in treating symptoms associated with menopause, particularly vasomotor symptoms and vaginal atrophy, without increasing the incidence of breast pain or overall AEs, including VTEs and cardiovascular AEs. Favorable effects on the lipid profile and minimal changes in coagulation and carbohydrate parameters were consistent with well known estrogen effects. Based on these findings, BZA/CE demonstrated a favorable benefit-risk profile and represents a promising new menopausal therapy with improved tolerability.

Acknowledgment: The authors acknowledge the contributions of the other investigators of the study (see Appendix).

REFERENCES

1. Population Division U.S. Census Bureau. Table 1: Annual estimates of the population by sex and five-year age groups for the United States: April 1, 2000 to July 1, 2007. NC-EST2007–01. May 2008.
2. Lobo RA, Belisle S, Creasman WT, Frankel NR, Goodman NE, Hall JE, et al. Should symptomatic menopausal women be offered hormone therapy? Med Gen Med 2006;8:1.
3. National Osteoporosis Foundation. Fast Facts. Available at http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed January 29, 2007.
4. Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, Lewiecki EM, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 2008;23:525–35.
5. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, De Villiers TJ, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo- and active-controlled clinical trial. J Bone Miner Res 2008;23:1923–34.
6. Gruber C, Gruber D. Bazedoxifene (Wyeth). Curr Opin Investig Drugs 2004;5:1086–93.
7. Komm BS, Kharode YP, Bodine PV, Harris HA, Miller CP, Lyttle CR. Bazedoxifene acetate: a selective estrogen receptor modulator with improved selectivity. Endocrinology 2005;146:3999–4008.
8. Ronkin S, Northington R, Baracat E, Nunes MG, Archer DF, Constantine G, et al. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. Obstet Gynecol 2005;105:1397–404.
9. Miller CP, Harris HA, Komm BS. Bazedoxifene acetate. Drugs Future 2002;27:117–21.
10. Boudes P, Ronkin S, Korner P, Baracat E, Constantine G. Effects of bazeoxifene (TSE-424), a novel tissue selective estrogen receptor modulator (SERM), on the incidence of breast pain. Osteoporos Int 2003;14:S14.
11. Van Duren D, Ronkin S, Pickar J, Constantine G. Bazedoxifene combined with conjugated estrogens: a novel alternative to traditional home therapies. Fertil Steril 2006;86:S88–9.
12. Pickar JH, Yeh I-T, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril 2009;92:1018–24.
13. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex (TSEC) of bazedoxifene/conjugated estrogens (BZA/CE) for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 2009;92:1045–52.
14. Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. Fertil Steril 2009;92:1039–44.
15. Walton C, Godsland IF, Proudler AJ, Wynn V, Stevenson JC. The effects of the menopause on insulin sensitivity, secretion and elimination in non-obese, healthy women. Eur J Clin Invest 1993;23:466–73.
16. Spencer CP, Godsland IF, Stevenson JC. Is there a menopausal metabolic syndrome? Gynecol Endocrinol 1997;11:341–55.
17. Lobo RA. Lipids, clotting factors, and diabetes: endogenous risk factors for cardiovascular disease. Am J Obstet Gynecol 1988;158:1584–91.
18. Mosca L, Grundy SM, Judelson D, King K, Limacher M, Oparil S, et al. Guide to preventive cardiology for women. AHA/ACC Scientific Statement Consensus Panel statement. Circulation 1999;99:2480–4.
19. Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. Ann Epidemiol 1992;2:161–76.
20. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. Arch Intern Med 1993;153:2209–16.
21. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E. Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. The Menopause Study Group. Obstet Gynecol 1994;84:987–95.
22. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. J Am Med Assoc 1995;273:199–208.
23. Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. Fertil Steril 2001;76:13–24.
24. Shlipak MG, Simon JA, Vittinghoff E, Lin F, Barrett-Connor E, Knopp RH, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. J Am Med Assoc 2000;283:1845–52.

APPENDIX

INVESTIGATOR LIST, SMART-1 STUDY

Mark Akin, M.D.
CEDRA Clinical Research.
Austin, Texas.

David Archer, M.D.
Eastern Virginia Medical School.
Norfolk, Virginia.

Gloria Bachmann, M.D.
Robert Wood Johnson Medical School.
University of Medicine and Dentistry of New Jersey.
New Brunswick, New Jersey.

Edmund Baracat, M.D.
Hospital do rim e Hipertenassao Fundacao.
Sao Paulo, Brazil.

Thomas Benninger, M.D.
Bluegrass Clinical Research, Inc.
Louisville, Kentucky.

Murray Berger, M.D.
Radiant Research–Las Vegas.
Las Vegas, Nevada.

Richard Beyerlein, M.D.
Pacific Women's Center, LLC.
Eugene, Oregon.

Verdayne Brandenburg, M.D.
Sioux Valley Clinic.
Sioux Falls, South Dakota.

Kirk Brody, M.D.
ClinSearch.
Chattanooga, Tennessee.

Michael Burnette, M.D.
Tampa Medical Group, P.A.
Tampa, Florida.

David G. Chaffin, Jr., M.D.
Marshall University Medical Center.
Huntington, West Virgina.

Bryan Cowan, M.D.
University of Mississippi Medical Center.
Jackson, Mississippi.

Uel Crosby, M.D.
U.T. Southwestern Medical Center.
Dallas, Texas.

Florenzo De Cicco Nardone, M.D.
Universita Cattolica del Sacro Cuore Istituto di
Clinica Ostetrica e Ginecologica.
Rome, Italy.

Domenico DeAloyisio, M.D.
Universita degli Studi di Bologna.
Bologne, Italy.

Janet Dietrich, M.D.
Montana Health Research Institute.
Billings, Montana.

Peter Dietze, Jr., M.D.
Women's Health Care at Frost Street.
San Diego, California.

James Dockery, M.D.
Drug Research & Analysis Corporation.
Montgomery, Alabama.

Costante Donati Sarti, M.D.
Azienda Ospedaliera Perugina Policlinico Monteluce.
Perugia, Italy.

Maxine Dorin, M.D.
University of New Mexico Hospital.
Albuquerque, New Mexico.

Kyrin Dunston, M.D.
Womancare Obstetrics & Gynecology, PC.
Savannah, Georgia.

Mildred Farmer, M.D.
Meridian Research.
St. Petersburg, Florida.

Jan Faska, M.D.
NZOZ Medical.
Katowice, Poland.

Robert Feldman, M.D.
Miami Research Associates, Inc.
Miami, Florida.

Carol Feltheim, M.D.
College Park Family Care Center.
Overland Park, Kansas.

Susan Floyd, M.D.
Primary Physicians Research, Inc.
Wexford, Pennsylvania.

Sandra Force-Obrowki, M.D.
Investigative Clinical Research.
Rancho Cucamonga, California.

Hendrik Robert Franke, M.D.
Medisch Spectrum Twente Hospital Group.
Enschede, the Netherlands.

J. Christopher Gallagher, M.D.
Creighton University Medical School.
Omaha, Nebraska.

Nicola Garcea, M.D.
Azienda Ospedaliera S. Giovanni Addolorata.
Rome, Italy.

Margery Gass, M.D.
Reproductive Medicine Research.
Holmes Hospital.
Cincinnati, Ohio.

David Gearhart, M.D.
New Ballas OB-GYN.
Creve Coeur, Missouri.

Andrea R. Genazzani, M.D.
Universita degli Studi di Pisa.
Pisa, Italy.

Catherine Gerrish, M.D.
Brown Clinic, PLLP.
Watertown, South Dakota.

Robert Greene, M.D.
Specialty Care for Women.
Redding, California.

Richard Godt, M.D.
ClinPhase Research, LLC.
Upland, California.

Charles Goldsmith, M.D.
Clinical Research Institute of South Florida.
Aventura, Florida.

Misericordia Guinot, M.D.
Hospital de la Sta. Creu i San Pau.
Barcelona, Spain.

Virginia Hall, M.D.
Milton S. Hershey Medical Center.
Hershey, Pennsylvania.

L. Clay Harrell, M.D.
Metrolina Medical Research.
Charlotte, North Carolina.

Bryan Hecht, M.D.
Mercy Medical Center.
Canton, Ohio.

Jorma Heikkinen, M.D.
Deaconess Institute.
Osteoporosis Clinic.
Oulu, Finland.

Lester Ho, M.D.
The Medical Group of Northern Nevada.
Reno, Nevada.

Hans-Olav Hoivik, M.D.
Hedmark Medisinske Senter AS.
Harmar, Norway.

Mary Holm, M.D.
Odyssey Research Services.
Fargo, North Dakota.

Terrence Horrigan, M.D.
Medical College of Ohio.
Toledo, Ohio.

Joseph Hume, M.D.
University of Kansas Medical Center.
Kansas City, Kansas.

William M. Johnson, III, M.D.
OB/GYN Associates of Alabama.
Birmingham, Alabama.

Risa Kagan, M.D.
Foundation for Osteoporosis Research and Education.
Oakland, California.

Bruce Kahn, M.D.
Scripps Clinic.
La Jolla, California.

Bruce Kessel, M.D.
Queen Emma Outpatient Center.
Honolulu, Hawaii.

Douglas Kiel, M.D.
Beth Israel Deaconess Medical Center.
Boston, Massachusetts.

Ellen Kim, M.D.
Albuquerque Clinical Trials, Inc.
Albuquerque, New Mexico.

Scott Kleber, M.D.
Laureate Clinical Research Group.
Atlanta, Georgia.

Michael Kleerekoper, M.D.
University Women's Care.
Southfield, Michigan.

Philippe Koninckx, M.D.
University Hospital Gasthuisberg.
Leuven, Belgium.

Gary Kraus, M.D.
East Coast Clinical Research.
Salisbury, Massachusetts.

Samuel Lederman, M.D.
Radiant Research, Inc.
West Palm Beach, Florida.

Vivian Lewis, M.D.
University of Rochester.
Medical Center.
Rochester, New York.

Gary Lipscomb, M.D.
UT Medical Group.
Memphis, Tennessee.

Rogerio Lobo, M.D.
Columbia University.
New York, New York.

Steven London, M.D.
Center for Fertility & Reproductive Health.
Shreveport, Louisiana.

Jose Lopez-Cintron, M.D.
Coastal Clinical Research.
Orange City, Florida.

Mel Lucas, D.O.
Patterson Medical Clinic.
PrimeCare Research Associates.
Florissant, Missouri.

James Lyle, M.D.
Alabama Clinical Therapeutics.
Birmingham, Alabama.

Raymond Malamet, M.D.
The Osteoporosis and Clinical Trials Center.
Hagerstown, Maryland.

Abe Marcadis, M.D.
Comprehensive NeuroScience, Inc.
Boynton Beach, Florida.

Phyllis Marx, M.D.
Radiant Research–Chicago.
Chicago, Illinois.

Diane Merritt, M.D.
Washington University.
St. Louis, Missouri.

Paul Miller, M.D.
GHS–Center for Women's Medicine.
Greenville, South Carolina.

Sam Miller, M.D.
SAM Clinical Research Center.
San Antonio, Texas.

Valerie Montgomery-Rice, M.D.
Meharry Medical College.
Nashville General Hospital Clinical Research Center.
Nashville, Tennessee.

Arnold Moses, M.D.
SUNY Upstate Medical University.
Institute for Human Performance.
Syracuse, New York.

Ken Muse, M.D.
University of Kentucky.
Lexington, Kentucky.

Manubai Nagamani, M.D.
University of Texas Medical Branch.
Galveston, Texas.

Robert Nordland, M.D.
Western OB/GYN.
Ridgeview Research.
Chaska, Minnesota.

Dale Osterling, M.D.
The Florida Wellcare Alliance, LC.
Inverness, Florida.

Santiago Palacios, M.D.
Instituto Palacios de Salud y Medicina de la Mujer.
Madrid, Spain.

Robert Parker, M.D.
Lyndhurst Gynecologic Associates.
Winston-Salem, North Carolina.

Tomasz Pertynski, Professor.
Klinika Ginekologii I Chorob Menopauzy.
Lodz, Poland.

JoAnn Pinkerton, M.D.
University of Virginia Health System.
Northridge Midlife Health Center.
Charlottesville, Virginia.

Larry Popeil, M.D.
Magnolia Research Group, Inc.
Ocala, Florida.

Bruno Pornel, M.D.
Brussels Menopause Center (BMC).
Brussels, Belgium.

Elizabeth Puscheck, M.D.
University Women's Care, Inc.
Southfield, Michigan.

Harvey Resnick, M.D.
R/D Clinical Research, Inc.
Lake Jackson, Texas.

Melvin Robinson, M.D.
Radiant Research, Inc.
Pinellas Park, Florida.

Daniel Rowe, M.D.
Palm Beach Research Center.
West Palm Beach, Florida.

John Rubino, M.D.
Triangle Medical Research Associates.
Raleigh, North Carolina.

Rebecca Ryder, M.D.
Mid-Atlantic Women's Care, PLC.
Chesapeake, Virginia.

Joseph Sanfilippo, M.D.
Magee Women's Hospital.
Pittsburgh, Pennsylvania.

Allan Sawyer, M.D.
HOPE Research Institute, LLC.
Phoenix, Arizona.

Sherwyn Schwartz, M.D.
Diabetes & Glandular Disease Research Associates, P.A.
San Antonio, Texas.

Eric Sheldon, M.D.
Miami Research Associates, Inc.
Miami, Florida.

Marek Sienkiewicz, M.D.
Skandynawskie Centrum Medyczne.
Wroclaw, Poland.

Wilma Smit, M.D.
Gemini Hospital.
Den Helder, the Netherlands.

Robert Smith, M.D.
Suncoast Clinical Research, Inc.
New Port Richey, Florida.

Rodney Smith, M.D.
Arizona Wellness Center for Women.
Phoenix, Arizona.

William B. Smith, M.D.
New Orleans Center for Clinical Research.
New Orleans, Louisiana.

Erik Snorre Ofjord, M.D.
Center for Clinical Trials.
Paradis (Bergen), Norway.

Marek Spaczynski, Professor.
Ginekologii I Poloznictwa Akademii.
Poznan, Poland.

Ronald Spencer, M.D.
Renstar Medical Research.
Ocala, Florida.

Leon Speroff, M.D.
Oregon Health & Science University.
Portland, Oregon.

Daniel Spratt, M.D.
OB/GYN Associates.
Portland, Maine.

Dale A. Sundwall, M.D.
Salt Lake Women's Center, PC.
Sandy, Utah.

Nancy Teaff, M.D.
REACH.
Charlotte, North Carolina.

Pawel Teter, M.D.
Krajowe Centrum Osteoporozy.
Warszawa, Poland.

Janusz Tomaszewski, M.D.
Private Clinic of Obstetrics and Gynaecology.
Bialystok, Poland.

Daniel Tomlinson, M.D.
Medford Women's Clinic, LLP.
Medford, Oregon.

Suzanne Trupin, M.D.
Women's Health Practice.
Champaign, Illinois.

Marjo Tuppurainen, M.D.
Laakariasema Cantti.
Kuopio, Finland.

Wulf Utian, M.D., Ph.D., D.Sc.(Med)
Rapid Medical Research, Inc.
Cleveland, Ohio.

Dyonne van Duren, M.D.
Menox.
Nijmegen, the Netherlands.

Richard Wasnich, M.D.
Radiant Research–Honolulu.
Honolulu, Hawaii.

Lynn Westphal, M.D., Ph.D.
Stanford University Medical Center.
Stanford, California.

Robert Wild, M.D.
University of Oklahoma.
Health Sciences Center.
Oklahoma City, Oklahoma.

R. Stan Williams, M.D.
University of Florida.
Women's Health at Magnolia Park.
Gainesville, Florida.

Kathryn Witzeman, M.D.
Denver Health Center.
Women's Care Clinic.
Denver, Clorado.

Grattan Woodson, III, M.D.
Atlanta Research Center.
Decatur, Georgia.

Mary Yankaskas, M.D.
Clinical Physiology Associates.
Clinical Study Center.
Ft. Myers, Florida.