Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women

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Objective: To evaluate the effect of bazedoxifene/conjugated estrogens (BZA/CE), a tissue selective estrogen complex, on uterine bleeding in postmenopausal women.
Design: International, multicenter, randomized, double-blind, placebo- and active-controlled, phase III study (Selective estrogen Menopause And Response to Therapy [SMART]-1).
Setting: Outpatient clinical.
Patient(s): Healthy, postmenopausal women (N = 3,397) aged 40 to 75 years with an intact uterus.
Intervention(s): Daily oral therapy with BZA 10, 20, or 40 mg, each with CE 0.625 or 0.45 mg, raloxifene 60 mg, or placebo.
Main Outcome Measure(s): Cumulative amenorrhea profiles and the incidence of bleeding or spotting over 2 years.
Result(s): Treatment with BZA 20 or 40 mg with CE 0.625 or 0.45 mg was associated with rates of cumulative amenorrhea (>83% during cycles 1–13 and >93% during cycles 10–13) and bleeding or spotting that were comparable to those with placebo. Subjects who received BZA 10 mg/CE 0.625 mg experienced slightly lower cumulative amenorrhea rates throughout the study compared with placebo-treated subjects.
Conclusion(s): Postmenopausal women treated with BZA 20 or 40 mg with CE 0.625 or 0.45 mg had high rates of cumulative amenorrhea that were similar to those reported with placebo. This new menopausal therapy may offer a favorable bleeding and tolerability profile. (Fertil Steril® 2009;92:1039–44. ©2009 by American Society for Reproductive Medicine.)

Key Words: Bazedoxifene, conjugated estrogens, BZA/CE, amenorrhea, uterine bleeding, tissue selective estrogen complex, TSEC, postmenopausal

The menopausal transition and the concomitant decline in estrogen levels may be associated with a host of undesirable symptoms and an increase in the risk of disease, particularly osteoporosis (1, 2). Both estrogen therapy (ET), which consists of estrogen alone, and hormone therapy (HT), which combines estrogen and progestogen, have shown efficacy in the relief of menopausal symptoms and prevention of osteoporosis (3, 4). However, HT is recommended for women with an intact uterus because ET alone is associated with endometrial stimulation (5–7). Evidence suggests that irregular bleeding and breast symptoms that occur during treatment with HT are common reasons for discontinuation during the first 2 years of therapy (8, 9). Thus, there remains an ongoing need for new therapies that may offer an improved vaginal bleeding and tolerability profile along with management of postmenopausal symptoms in women with an intact uterus.

Bazedoxifene (BZA) is a novel selective estrogen receptor modulator (SERM) undergoing clinical development for the prevention and treatment of postmenopausal osteoporosis. Results of preclinical studies using rodent models suggest that BZA alone has little to no endometrial stimulation and potently antagonizes conjugated estrogen (CE)-induced stimulation of the endometrium when coadministered (10). Treatment with BZA in several rodent models had a neutral effect on the endometrium and did not inhibit the beneficial vasomotor effects of 17β-estradiol (E_2) at a bone-sparing dose (11, 12). Preclinical studies (11, 12) also showed that BZA inhibits 17β-E_2–induced proliferation of MCF-7 human breast cancer cells in a dose-dependent manner. Daily doses of 2.5, 5.0, 10, 20, 30, and 40 mg BZA in a phase II study (13) were generally well tolerated and were not associated with endometrial stimulation compared with placebo. Further, BZA 30 and 40 mg were associated with significantly smaller mean increases in endometrial thickness and significant decreases in uterine bleeding compared with placebo ($P<.05$) (13), suggesting estrogen antagonist activity in the endometrium.

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Portions of this work were presented at the 89th Annual Meeting of the Endocrine Society; June 2–5, 2007; Toronto, Ontario, Canada. Abstract P1-350.
The Selective estrogen Menopause And Response to Therapy (SMART)-1 trial was a 2-year, outpatient, randomized, double-blind, placebo- and active-controlled, phase III study conducted at 94 sites in the United States, Europe, and Brazil (Unique trial number: NCT00675688; Trial registration date: 05/09/2008).
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A novel approach to the treatment of menopausal symptoms is the tissue selective estrogen complex (TSEC), which partners a SERM with one or more estrogens to achieve optimal clinical results based on their blended tissue-selective activity profile (14). The first TSEC in clinical development, BZA with CE, is based on the endometrial protective and tissue-selective properties of BZA observed in preclinical evaluations (10, 15). The interaction of BZA and CE in the individual tissues (breast, endometrium, bone, and lipid biosynthesis) appears to be unique to this TSEC and not replicated with progestins or other SERMs (10, 16, 17). Raloxifene, another SERM, has shown differential outcomes in a rodent model compared with BZA; such a finding highlights the subtle but real differences in the molecular and morphologic effects of individual SERMs (17, 18). Although clinical trials evaluating E_2 or esterified estrogens paired with raloxifene have shown relief of menopausal symptoms with the addition of estrogens, there was a significant increase in the incidence of endometrial hyperplasia and endometrial thickening (19–21).

The Selective estrogen Menopause And Response to Therapy-1 (SMART-1) trial evaluated the efficacy and safety of BZA/CE in postmenopausal women with a uterus over a 2-year period. Findings from this study showed that BZA/CE was effective in preventing osteoporosis and providing relief of vasomotor and vaginal symptoms while ensuring endometrial safety. Treatment with BZA 20 mg/CE 0.625 or 0.45 mg was associated with low rates (<1%) of endometrial hyperplasia that were not significantly different compared with placebo for up to 2 years. Furthermore, changes from baseline in endometrial thickness observed with BZA 20 mg/CE 0.625 or 0.45 mg were similar to those with placebo at 1 or 2 years. Details of the effects of BZA/CE on these parameters are described in separate reports in this journal (22–24). The endpoints related to the incidence of uterine bleeding and cumulative amenorrhea profiles associated with BZA/CE will be described herein.

MATERIALS AND METHODS

Subjects

Subjects eligible for study enrollment were generally healthy women ages 40 to 75 years who were postmenopausal as indicated by having completed their last natural menstrual cycle at least 12 months before screening and by having specified serum concentrations of follicle-stimulating hormone ($\geq$30 mIU/mL) and 17β-E_2 ($\leq$183.5 pmol/L). At the screening visit, all subjects were required to have an intact uterus and acceptable endometrial histology, which was defined as one of the following: proliferative endometrium; weakly proliferative endometrium; secretory endometrium; endometrial tissue, other (including benign, inactive, or atrophic fragments of endometrial epithelium, glands, stroma, etc.); endometrial tissue insufficient for diagnosis; no endometrium identified; or no tissue identified. Subjects were required to have endometrium identified as sufficient for diagnosis by at least one of the two primary pathologists. Subjects with endometrial hyperplasia or malignancy were excluded from the study. Subjects were also required to have a body mass index $\leq$32.2 kg/m^2.

Subjects were excluded if they had a history or presence of known or suspected estrogen-dependent neoplasia; known hypersensitivity to estrogens; thromboembolic disease, cerebrovascular event, or ischemic heart disease; history of breast cancer, melanoma, or any gynecologic cancer; unresolved findings suggestive of malignant changes on the prestudy mammogram; certain unresolved or abnormal cervical smear results; or any endocrine disease except for controlled hypothyroidism. Subjects were prohibited from the use of any oral estrogen-, progestin-, androgen-, or SERM-containing medication, or any vaginal or transdermal hormonal product within 8 weeks before screening, any investigational drug within 60 days, an intrauterine device within 12 weeks, or any injectable or pelleted hormone product within 24 weeks.

Study Design

The SMART-1 trial was a 2-year, outpatient, multicenter, randomized, double-blind, placebo- and active- (raloxifene) controlled phase III study conducted in the United States, Europe, and Brazil. Subjects were assigned to one of eight treatments through the use of a computerized randomization/enrollment interactive voice recognition system: BZA 10, 20, or 40 mg, each with CE 0.625 or 0.45 mg, raloxifene 60 mg, or placebo. The randomization was balanced at site level, with a block size of 8. For blinding purposes, BZA/CE and raloxifene were provided as single tablets that were overencapsulated to match placebo capsules. Subjects were required to take one capsule orally each day for 2 years and to maintain a daily intake of dietary and supplemental calcium and vitamin D (total daily calcium intake of approximately 1,000–1,600 mg).

The protocol was approved by an independent ethics committee or an institutional review board at each site before study initiation. Informed consent forms were reviewed, and consent was obtained from all subjects before study enrollment.

The primary objective of this study was to evaluate the effects of BZA/CE on the incidence of endometrial hyperplasia in postmenopausal women after 1 year of therapy. Secondary objectives included evaluation of the efficacy of BZA/CE in preventing osteoporosis after 2 years of therapy and the effects of BZA/CE on safety, metabolic parameters (including lipids, serum bone turnover markers, carbohydrates, and coagulation factors), vaginal atrophy, vasomotor symptoms, and quality of life indices. These data are presented in separate reports in this journal (22–24). The objective of this report is to describe the effects of BZA/CE on cumulative amenorrhea profiles and the incidence of bleeding and spotting seen in this study.

Assessment of Amenorrhea, Bleeding, and Spotting

Each day, subjects were asked to record in a diary whether they experienced bleeding (sanitary protection required), spotting (no sanitary protection required), or no bleeding or spotting. Rates of amenorrhea, which was defined as the absence of bleeding or spotting, were determined for cumulative 4-week periods (i.e., cycles) throughout the 2-year study. Cumulative rates of amenorrhea were defined as the percentage of women who reported consecutive cycles of amenorrhea for a given period of time (25). The percentage of subjects with amenorrhea for each cumulative period was summarized separately for year 1 (cumulative rate of amenorrhea reported during the 1st through the 13th cycle) and year 2 (cumulative rate of amenorrhea reported during the 14th through the 26th cycle). Bleeding data were also summarized in a noncumulative manner as the incidence of bleeding or spotting and the mean number of bleeding or spotting days for each cycle.

Endometrial biopsy was performed at screening and at 6, 12, and 24 months as part of the endometrial safety evaluation (primary endpoint). Bleeding data collected for the day on which an endometrial biopsy was performed and for the 6 days thereafter were excluded for both cumulative and noncumulative summaries. The last available data before the biopsy was performed were carried forward for those days in a last observation carried forward approach.

Adverse Bleeding Events

Subjects were instructed to record information related to adverse events (AEs) in a daily diary. The number and percentage of subjects reporting each type of AE were summarized. Bleeding and spotting AEs were classified as "uterine hemorrhage" or "vaginal hemorrhage" as defined by the Medical Dictionary for Regulatory Activities and based on the verbatim term used by the investigator when reporting the AE. Data were evaluated for all AEs that began during or after treatment.

Statistical Analyses

Cumulative amenorrhea profiles and the incidence of bleeding or spotting were assessed using two populations: the modified intent-to-treat (MITT) population and the efficacy evaluable (EE) population. For analyses of cumulative amenorrhea, both populations included subjects who took at least one dose of the study drug, but subjects in the MITT population had to have at least 1 day of on-therapy bleeding data. For analyses of the noncumulative

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