Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women

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Objective: To evaluate the efficacy of the tissue-selective estrogen complex, bazedoxifene/conjugated estrogens (BZA/CE), for postmenopausal osteoporosis prevention.
Design: Multicenter, randomized, double-blind, placebo- and active-controlled, phase 3 trial (Selective estrogen Menopause And Response to Therapy [SMART]-1).
Setting: Outpatient clinical study.
Patient(s): Women (n = 3,397) more than 5 years and 1–5 years postmenopause were enrolled in the Osteoporosis Prevention I and II Substudies, respectively.
Intervention(s): Single tablets of BZA (10, 20, or 40 mg) each with CE (0.625 or 0.45 mg), raloxifene (60 mg), or a placebo taken daily for 2 years.
Main Outcome Measure(s): The primary outcome for both substudies was change in bone mineral density of the lumbar spine; bone mineral density was also measured at the hip.
Result(s): In both substudies, bone mineral density increased significantly more with all BZA/CE doses compared with placebo at the lumbar spine and total hip, and for most BZA/CE doses compared with raloxifene at the lumbar spine. Osteocalcin and N-telopeptide significantly decreased with all BZA/CE doses vs. placebo and most BZA/CE doses vs. raloxifene.
Conclusion(s): BZA/CE combinations decreased bone turnover and bone loss in postmenopausal women at increased risk for osteoporosis. (Fertil Steril® 2009;92:1045–52. ©2009 by American Society for Reproductive Medicine.)

Key Words: Bazedoxifene, bone mineral density, conjugated estrogens, osteoporosis, tissue-selective estrogen complex

Estrogen deficiency in women at menopause can lead to significant bone loss and osteoporosis if not treated. One of the first-line therapies for preventing menopausal bone loss in symptomatic postmenopausal women is hormonal therapy, either estrogen alone or estrogen plus a progestin. Placebo-controlled studies indicate that various doses and regimens of conjugated estrogens (CEs) with or without medroxyprogesterone acetate (MPA) prevent bone loss in postmenopausal women (1–3). In particular, the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study demonstrated that lower doses of CE/MPA administered to early postmenopausal women significantly increased bone mineral density (BMD) at the lumbar spine and hip (2, 3). Subsequently, the large, placebo-controlled Women's Health Initiative showed that CE alone (0.625 mg) (4, 5) or CE (0.625 mg) combined with MPA (2.5 mg/d) (6, 7) significantly reduced the risk of vertebral and nonvertebral fractures and increased BMD.

In the search for therapies that could prevent postmenopausal bone loss with fewer hormone-related side effects, selective estrogen receptor modulators (SERMs) were developed. Currently, raloxifene is the only SERM approved for the prevention and treatment of postmenopausal osteoporosis. Clinical studies demonstrated that raloxifene significantly increases BMD of the lumbar spine and hip in postmenopausal women, and significantly reduces the risk of vertebral fractures and levels of bone turnover biomarkers (BTMs), but does not reduce the risk of nonvertebral fractures (8–11). Observed effects of raloxifene on BMD are also of smaller magnitude (8, 11) than those reported in separate studies for estrogen alone or estrogen plus a progestin (2).

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Clinical trial registration is available at http://www.ClinicalTrials.gov, NCT00675688.
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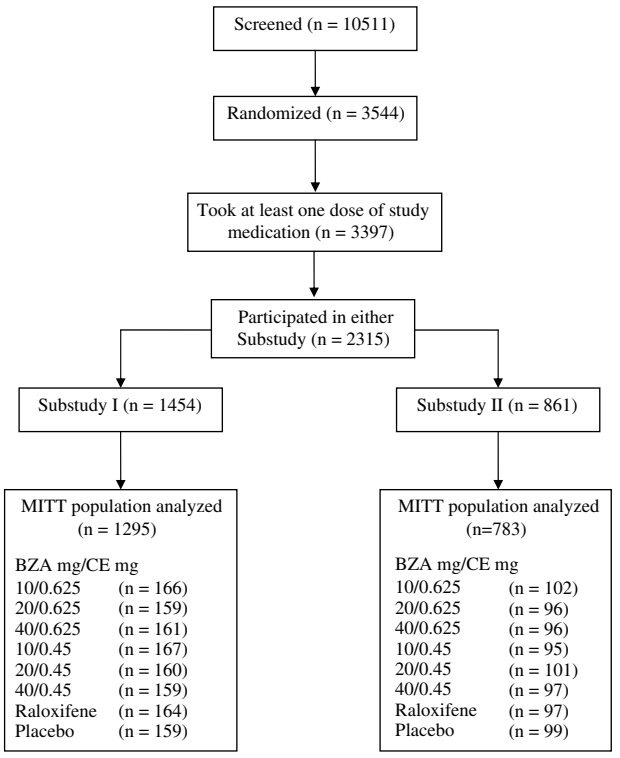
FIGURE 1

Subject disposition. Substudy I = women >5 years postmenopause; substudy II = women between 1 and 5 years postmenopause; BZA = bazedoxifene; CE = conjugated estrogen; MITT = modified intent to treat.



Lindsay. Preventing osteoporosis with BZA/CE. Fertil Steril 2009.

The concept of a tissue-selective estrogen complex (TSEC), or the pairing of a SERM with estrogens, was designed to improve on currently available menopausal therapies. The clinical profile of a TSEC would be based on the tissue-selective activities of both SERMs and estrogens. The ideal estrogen-SERM combination would have the positive attributes of both components without, or with fewer of, their undesired effects. An appropriate TSEC would alleviate hot flushes, treat vulvar and vaginal atrophy, and protect against bone loss without stimulating the endometrium.

Bazedoxifene (BZA) is a novel SERM that has been shown in preclinical studies to maintain bone mass and not to stimulate the endometrium (12, 13). In a phase 2 clinical study, BZA was well tolerated with endometrial thickness and amenorrhea rates comparable to those with placebo (14). Further, lumbar spine BMD was significantly greater with BZA than with placebo in a 2-year, randomized, double-blind, placebo-controlled trial (15), and the incidence of new vertebral fractures was significantly lower with BZA vs. placebo in a study of postmenopausal women with osteoporosis (16). Given these favorable data, a TSEC containing BZA and CE was designed as a potential new comprehensive menopausal therapy.

The primary objective of this study was to evaluate effects of a TSEC composed of various doses of BZA and CE on lumbar spine BMD with up to 2 years of use in postmenopausal women at risk for osteoporosis. The effects of BZA/CE on hip and radial BMD and on BTM were also investigated.

MATERIALS AND METHODS

Study Design

The Selective estrogen Menopause And Response to Therapy-1 (SMART) trial was a 2-year, multicenter, randomized, double-blind, and placebo- and active-controlled phase 3 study conducted at 94 sites in the United States, Europe, and Brazil (NCT00675688 at http://www.ClinicalTrials.gov). The main study evaluating the primary outcome of endometrial hyperplasia at 12 months, which will be reported elsewhere, was conducted at all sites. This report describes the results of two osteoporosis substudies. The Osteoporosis Prevention I Substudy (substudy I) examined women who were >5 years postmenopausal at 40 sites internationally. Because the rate of bone loss might be greater for women immediately after menopause compared to later years, BMD was also evaluated in women between 1–5 years postmenopausal in the Osteoporosis Prevention II and Metabolic Substudy (substudy II) conducted at 25 sites internationally. An independent ethics committee or institutional review board approved the protocol for each site.

Eligible screened subjects were randomly assigned to 1 of 8 treatment groups: BZA (10, 20, or 40 mg) each with CE (0.625 or 0.45 mg), raloxifene (60 mg), or placebo. Randomization was based on a schedule generated by Wyeth Research (Philadelphia, PA) and was implemented through the use of a computerized randomization and enrollment interactive voice recognition system. To maintain blinding, BZA/CE and raloxifene were provided as single tablets over-encapsulated to match placebo capsules. Subjects were directed to take one capsule orally at approximately the same time each day for 2 years. If necessary, subjects were assigned to supplemental calcium and vitamin D (Caltrate 600 with D) to maintain the target calcium intake requirement of 1,000–1,600 mg during the study. The amount of calcium and vitamin D supplementation provided, if any, was based on an assessment of their estimated daily calcium intake at the time of randomization.

The primary outcome for both substudies was change in BMD of the lumbar spine by dual-energy x-ray absorptiometry (DXA); secondary outcomes included BMD at hip sites and BTM.

Subjects

Generally healthy postmenopausal women aged 40–75 years with an intact uterus, body mass index $\leq$32.2 kg/m^2, and no evidence of endometrial hyperplasia at screening were eligible for the SMART-1 trial. Subjects were considered to be postmenopausal if they had completed their last menstrual cycle at least 1 year before screening and had serum FSH $\geq$30 mIU/mL and 17β-estradiol concentrations $\leq$50 pg/mL or 183.5 pmol/L. Additional primary inclusion and exclusion criteria are described elsewhere.

Substudy I enrolled women who were >5 years from their last natural menstrual period, had a screening BMD T-score at lumbar spine or total hip between –1 and –2.5 (inclusive), and had at least one additional risk factor for osteoporosis. Substudy II enrolled women who were 1–5 years from their last menstrual period with at least one risk factor for osteoporosis. Risk factors included family history of osteoporosis, early menopause ($\leq$40 years of age), currently smoking, history of excessive alcohol use, low-calcium diet, inactive lifestyle, thin and/or small frame (weight <50 kg and/or BMI <18 kg/m^2), Caucasian, or Asian. Subjects with lumbar spine or total hip BMD >2.5 standard deviations below the normal for healthy young women, a history of osteoporosis-related fracture, clinically active rheumatoid arthritis, or any disease that might affect bone metabolism were excluded.