The Tissue-Selective Estrogen Complex (TSEC): A Promising New Therapy for Menopausal Symptoms and Postmenopausal Osteoporosis

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Abstract The menopausal transition may be associated with bothersome symptoms and increased risk of osteoporosis that can decrease quality of life for women. The primary treatment option is hormone therapy, which has been associated with some safety and tolerability concerns. The tissue-selective estrogen complex (TSEC) is a novel therapy that pairs a selective estrogen receptor modulator with one or more estrogens. The first TSEC in clinical development partners bazedoxifene (BZA) with conjugated estrogens (CE) and has been evaluated in the phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART) trials. BZA 20 mg/CE 0.45 and 0.625 mg have been shown to be effective in reducing the frequency and severity of hot flashes and improving measures of vulvar/vaginal atrophy. These BZA/CE doses have also been shown to increase bone mineral density and reduce bone turnover without stimulating the endometrium and breast. BZA/CE represents a promising new therapy for postmenopausal women.

Keywords Menopause · Osteoporosis · Estrogen · Selective estrogen receptor modulator · SERM · Bazedoxifene · BZA/CE · Tissue-selective estrogen complex · TSEC · Safety · Efficacy · Hot flashes · Vasomotor symptoms · Vulvar/vaginal atrophy · Bone mass · Clinical trials

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Introduction

During the menopausal transition, women experience a decline in estrogen production [1] that may result in undesirable symptoms such as hot flashes and symptoms associated with vulvar/vaginal atrophy (VVA), as well as loss of bone mass leading to an increased risk of osteoporosis [2]. Vasomotor symptoms (VMS) and VVA can cause physical discomfort and interfere with sleep and daily activities, resulting in a decreased quality of life for postmenopausal women [2]. Additionally, development of postmenopausal osteoporosis increases the risk of bone fractures, which are associated with significant morbidity and increased mortality [3–5]. As the number of postmenopausal women worldwide continues to increase [6], menopause-related health issues can impose a significant social and economic burden. The management of menopausal symptoms and the treatment of menopause-related conditions are therefore global health concerns.

The established treatment options for menopausal symptoms include estrogen therapy (ET) and combined estrogen-progestin therapy (EPT) for postmenopausal women with an intact uterus. ET and EPT are indicated for the treatment of moderate to severe VMS and VVA and are also approved for the prevention of postmenopausal osteoporosis [7]. The inclusion of progestin in EPT is important for protecting the endometrium in nonhysterectomized women. However, EPT has been associated with some safety and tolerability concerns, including stimulation of the breast [8] and irregular vaginal bleeding [9, 10]. Thus, there is a need for new therapies with improved safety and tolerability profiles that can provide comprehensive relief of menopausal symptoms and preserve bone mass while ensuring endometrial and breast safety.

A novel therapy under development is the tissue-selective estrogen complex (TSEC), which partners a selective estrogen receptor modulator (SERM) with one or more estrogens

for a clinical profile that is a blend of the properties of the individual components [11]. An effective TSEC would combine the efficacy of estrogens in treating VMS and VVA and preventing osteoporosis with the protective effects of a SERM in the uterus and breast. Based on promising preclinical findings that bazedoxifene (BZA) inhibited estrogen-induced increases in rat uterine wet weight and stimulation of breast cancer cells [12–14], the pairing of BZA with conjugated estrogens (CE) was further evaluated in clinical studies and is the first TSEC in clinical development.

Clinical Studies of BZA/CE

BZA/CE has been evaluated in a series of multicenter, randomized, double-blind, placebo-controlled and active-controlled phase 3 trials known as the Selective estrogens, Menopause, And Response to Therapy (SMART) trials. Detailed methodology for these trials has previously been reported [15•, 16•, 17•]. The SMART-1 trial ($N=3,397$) was conducted at 94 sites in the United States, Europe, and Brazil and enrolled generally healthy, postmenopausal women 40 to 75 years of age [15•, 18•, 19•, 20•]. Eligible subjects had to have an intact uterus, a body mass index (BMI) ≤ 32.2 kg/m², and acceptable endometrial biopsy results at screening. This study evaluated the efficacy and safety of BZA 10, 20, and 40 mg/CE 0.45 and 0.625 mg compared with those of raloxifene 60 mg and placebo over 2 years of treatment. The primary endpoint was the incidence of endometrial hyperplasia at 1 year; secondary endpoints included changes from baseline in bone mineral density (BMD), serum bone turnover marker levels, and the frequency and severity of hot flushes. Based on results from this trial showing that BZA 20 mg is the lowest effective dose for protecting the endometrium from estrogen stimulation [20•], the doses selected for evaluation in the subsequent SMART-2 and SMART-3 trials were BZA 20 mg/CE 0.45 and 0.625 mg.

The SMART-2 trial ($N=318$) was conducted at 43 sites in the United States and enrolled healthy, postmenopausal women 40 to 65 years of age with an intact uterus and a BMI ≤ 34.0 kg/m² [16•, 21]. Eligible subjects had to have 7 or more moderate to severe hot flushes daily (or at least 50 per week) at screening and be seeking treatment for hot flushes. This study evaluated the effects of BZA 20 mg/CE 0.45 and 0.625 mg on VMS compared with the effects of placebo over 12 weeks of treatment. The primary endpoint was the change from baseline in the frequency and severity of hot flushes. Secondary endpoints included effects on sleep, quality of life, and satisfaction with treatment.

The SMART-3 trial ($N=652$) was conducted at 66 sites in the United States and enrolled generally healthy, postmenopausal women 40 to 65 years of age with an

intact uterus and a BMI ≤ 34.0 kg/m² [17•, 22]. All women had to have a vaginal cytologic smear showing no more than 5% superficial cells, a vaginal pH higher than 5, and at least one moderate to severe VVA symptom at screening. This study examined the effects of BZA 20 mg/CE 0.45 and 0.625 mg compared with those of BZA 20 mg and placebo on measures of VVA over 12 weeks of treatment. Secondary endpoints included the impact on sexual function, quality of life, and satisfaction with treatment.

Efficacy on Vasomotor Symptoms

In the SMART-1 trial, the efficacy of BZA/CE on VMS was evaluated in a subgroup of women with 7 or more moderate to severe hot flushes per day at baseline ($n=216$) [15•]. All doses of BZA/CE (BZA 10, 20, and 40 mg/CE 0.45 and 0.625 mg) showed a significantly greater reduction from baseline in the mean daily number of moderate to severe hot flushes than placebo at weeks 5 to 12 ($P<0.05$; Table 1). At 12 weeks, BZA/CE reduced the mean daily number of hot flushes from baseline by 51.7% to 85.7%, compared with 17.1% for placebo. There was also a significantly greater reduction from baseline in the mean severity of hot flushes compared with placebo at weeks 4 and 12 for the groups taking BZA 10 mg/CE 0.45 or 0.625 mg and at week 12 for the groups taking BZA 20 mg/CE 0.45 or 0.625 mg ($P<0.001$; Table 1). Additionally, BZA 10 and 20 mg/CE 0.45 and 0.625 mg showed significantly greater reductions in the frequency and severity of hot flushes compared with raloxifene 60 mg at weeks 6 to 12. The improvement in VMS with BZA 10 and 20 mg/CE 0.45 and 0.625 mg versus placebo was sustained over 2 years of therapy [15•, 23].

In the SMART-2 trial, the effects of BZA 20 mg/CE 0.45 and 0.625 mg on VMS were evaluated in randomized subjects who received at least one dose of their assigned study medication and recorded 5 or more days of data each during the baseline week and at least one on-therapy week. Both BZA/CE groups showed a significantly greater decrease in the mean daily number of moderate to severe hot flushes compared with placebo at weeks 3 to 12 ($P<0.01$; Table 1 and Fig. 1) [16•]. At week 12, BZA 20 mg/CE 0.45 and 0.625 mg reduced the mean daily number of hot flushes from baseline by 74% and 80%, respectively, compared with 51% for placebo. BZA 20 mg/CE 0.45 and 0.625 mg also showed a significantly greater decrease in the mean severity of hot flushes compared with placebo at weeks 3 to 12 ($P<0.001$). Moreover, significantly higher percentages of subjects in the BZA/CE groups had at least a 50% or 75% reduction in the number of moderate to severe hot flushes at weeks 4 and 12 compared with placebo ($P<0.001$). The proportion of women with at least a 75% reduction at week 12 was 61% for BZA 20 mg/CE

Table 1 Effects of BZA/CE on vasomotor and VVA symptoms and bone

SMART-1	SMART-2	SMART-3
<i>Efficacy on vasomotor and VVA symptoms</i>		
<ul style="list-style-type: none"> Significant decrease from baseline in the mean daily number and severity of hot flushes at week 12 for BZA 10 and 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [15••] Significant increase in the proportion of superficial and intermediate cells and decrease in the proportion of parabasal cells from baseline at 2 years for BZA 10 mg/CE 0.45 and 0.625 mg and BZA 20 mg/CE 0.625 mg vs PBO ($P<0.01$) [15••] 	<ul style="list-style-type: none"> Significant decrease from baseline in the mean daily number and severity of hot flushes at weeks 3–12 for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.01$) [16•] 	<ul style="list-style-type: none"> Significant increase in the proportion of superficial and intermediate cells and decrease in the proportion of parabasal cells from baseline at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [17•] Significant decrease from baseline in vaginal pH and improvement in the most bothersome VVA symptom at 12 weeks for BZA 20 mg/CE 0.625 mg vs PBO ($P<0.05$) [17•]
<i>Effects on bone</i>		
<ul style="list-style-type: none"> Significant increase from baseline in lumbar spine and total hip BMD at months 6, 12, 18, and 24 for BZA 10, 20, and 40 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [19•] Significant decrease from baseline in serum BTM levels at months 6, 12, 18, and 24 for BZA 10, 20, and 40 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.001$) [19•] 	N/A	N/A

BZA bazedoxifene, CE conjugated estrogens, SMART Selective estrogens, Menopause, And Response to Therapy, VVA vulvar/vaginal atrophy, PBO placebo, BMD bone mineral density, N/A not available, BTM bone turnover marker

0.45 mg and 73% for BZA 20 mg/CE 0.625 mg, compared with 27% for placebo.

Efficacy on Vulvar/Vaginal Atrophy

The SMART-1 trial assessed measures of VVA in a subgroup of women with no more than 5% superficial cells at screening

and who had a baseline and at least one on-therapy assessment ($n=1,867$) [15••]. At 24 months, the groups given BZA 10 mg/CE 0.45 or 0.625 mg or BZA 20 mg/CE 0.625 mg showed a significantly greater increase from baseline in the mean proportion of superficial cells compared with placebo ($P<0.01$; Table 1). BZA 10 and 20 mg/CE 0.45 and 0.625 mg also resulted in a greater increase in the mean proportion of

Fig. 1 Effects of BZA/CE on the mean daily number of hot flushes over 12 weeks.

Reprinted by permission from Wolters Kluwer Health: Menopause [16•], copyright 2009. The mean daily number of hot flushes was significantly lower compared with placebo for both BZA/CE doses at weeks 3 to 12 ($P<0.01$) and for BZA 20 mg/CE 0.625 mg at week 2 ($P<0.01$). BZA bazedoxifene, CE conjugated estrogens, PBO placebo

intermediate cells and a greater decrease in the mean proportion of parabasal cells from baseline compared with placebo ($P<0.001$) at 24 months. Compared with placebo or raloxifene 60 mg, there was a significantly lower incidence of dyspareunia for BZA 10 mg/CE 0.625 mg at weeks 5 to 8 ($P<0.05$) and for BZA 10 mg/CE 0.625 mg and BZA 20 mg/CE 0.45 and 0.625 mg at weeks 9 to 12 ($P<0.05$).

In the SMART-3 trial, the efficacy of BZA 20 mg/CE 0.45 and 0.625 mg on VVA was evaluated in subjects who received at least one dose of their assigned study medication and had at least one baseline and one on-therapy value for the parameter being assessed [17•]. At 12 weeks, the groups receiving BZA 20 mg/CE 0.45 or 0.625 mg showed a significantly greater increase from baseline in the mean proportion of superficial cells compared with placebo or BZA 20 mg ($P<0.01$; Table 1). Both BZA/CE groups also showed a significantly greater reduction from baseline in the mean proportion of parabasal cells ($P<0.001$) and a significantly greater increase from baseline in the mean proportion of intermediate cells ($P<0.05$) compared with placebo or BZA 20 mg at weeks 4 and 12. Additionally, treatment with BZA 20 mg/CE 0.625 mg resulted in a significantly greater decrease from baseline in vaginal pH ($P<0.001$) and a greater improvement in the women's most bothersome VVA symptom ($P<0.05$) compared with placebo or BZA 20 mg at week 12 (Table 1). When individual vaginal symptoms were assessed, BZA 20 mg/CE 0.45 and 0.625 mg significantly improved vaginal dryness at 12 weeks compared with BZA 20 mg ($P\leq 0.001$) and placebo ($P<0.05$). At 12 weeks, both BZA/CE groups had significantly higher percentages of responders, defined as women with greater than 5% superficial cells, vaginal pH lower than 5, and/or improvement from baseline in the most bothersome VVA symptom by at least one category, compared with the groups given BZA 20 mg or placebo. The responder rate was 78% for BZA 20 mg/CE 0.45 mg; 81% for BZA 20 mg/CE 0.625 mg; 58% for BZA 20 mg; and 66% for placebo ($P<0.001$ vs BZA 20 mg and $P<0.05$ vs placebo).

Effects on Bone

The SMART-1 trial included two osteoporosis substudies assessing the effects of BZA 10, 20, and 40 mg/CE 0.45 and 0.625 mg on bone. Substudy I ($n=1,454$) enrolled women whose last menstrual period was more than 5 years prior to screening and who had a BMD T-score between -1 and -2.5 at screening and at least one additional risk factor for osteoporosis. Substudy II ($n=861$) enrolled women whose last menstrual period was between 1 and 5 years prior to screening and who had at least one risk factor for osteoporosis [19•]. For both substudies, all BZA/CE doses showed significantly greater increases from baseline in lumbar spine BMD at

months 6, 12, 18, and 24 compared with placebo ($P<0.001$; Table 1). The adjusted annual percentage change from baseline in lumbar spine BMD for the BZA/CE groups ranged from 0.51% to 1.59%, compared with -1.08% for placebo in Substudy I ($P<0.001$ vs placebo for all), and from 0.55% to 1.60% compared with -1.41 for placebo in Substudy II ($P<0.001$ vs placebo for all). The percentage of responders for lumbar spine BMD (defined as women with either no change or an increase from baseline in lumbar spine BMD at 12 and 24 months) was significantly higher in all BZA/CE groups compared with placebo ($P<0.001$) in both substudies: responder rates at month 24 were 63% to 76% for BZA/CE versus 30% for placebo in Substudy I and 61% to 76% for BZA/CE versus 31% for placebo in Substudy II. All BZA/CE groups in both substudies also showed significantly greater improvement from baseline in lumbar spine BMD at 24 months compared with raloxifene 60 mg ($P<0.05$), except for BZA 40 mg/CE 0.45 and 0.625 mg in Substudy I.

All BZA/CE doses showed significantly greater increases from baseline in total hip BMD at months 6, 12, 18, and 24 compared with placebo ($P<0.05$) in both substudies (Table 1). In Substudy I, significantly greater increases from baseline in BMD at the femoral intertrochanteric, neck, and trochanteric regions were seen for all BZA/CE groups compared with placebo at months 12 and 24 ($P<0.001$). Similarly, all BZA/CE groups in Substudy II showed significantly greater increases from baseline in BMD at these skeletal sites compared with placebo at months 12 and 24 ($P<0.05$), except for BZA 40 mg/CE 0.45 mg at the femoral neck at 12 months. Significantly greater improvement from baseline in total hip BMD at 24 months compared with raloxifene 60 mg ($P<0.05$) was observed for BZA 10 mg/CE 0.45 and 0.625 mg and BZA 20 mg/CE 0.625 mg in Substudy I and for BZA 10 mg/CE 0.45 and 0.625 mg, BZA 20 mg/CE 0.45 mg, and BZA 40 mg/CE 0.625 mg in Substudy II.

The effects of BZA/CE on bone turnover were evaluated in women between 1 and 5 years from menopause (Substudy II) based on the change in serum levels of osteocalcin (OC) and C-telopeptide (CTx). All BZA/CE groups showed a significantly greater reduction from baseline in serum OC and CTx levels compared with placebo at months 6, 12, 18, and 24 ($P<0.001$). At month 24, the median percent change from baseline in serum OC levels ranged from -19.78% to -28.05% for the BZA/CE groups compared with 3.08% for placebo; the change in CTx levels ranged from -42.72% to -53.40% for the BZA/CE groups compared with -13.81% for placebo. The median percentage changes from baseline in serum levels of these markers were also significantly greater for all BZA/CE doses than for raloxifene 60 mg ($P<0.05$) at 24 months, except for BZA 40 mg/CE 0.625 mg for OC at 6 months and BZA 40 mg/CE 0.45 mg for CTx at 24 months.

Safety and Tolerability

Endometrial Safety

In the SMART-1 trial, the BZA 20- or 40-mg/CE 0.45- or 0.625-mg groups all had low rates of endometrial hyperplasia (<1%) at 24 months, similar to the rates observed for placebo (Table 2) [20••]. These BZA/CE doses also showed minimal increases from baseline in endometrial thickness (<1 mm) at 24 months, which were similar to the increases observed for placebo. In contrast, the groups receiving BZA 10 mg/CE 0.45 or 0.625 mg had endometrial hyperplasia rates of 2.53% and 7.14% at 24 months, respectively, and showed significantly greater increases from baseline in endometrial thickness compared with placebo ($P<0.01$). These data demonstrated that BZA 20 mg was the lowest dose that effectively protected the endometrium from stimulation. Consistent with these findings, the SMART-2 trial showed no significant difference between the BZA 20-mg/CE 0.45- and 0.625-mg groups and the placebo group in the mean change from baseline in endometrial thickness at week 12 (Table 2) [16•]. The percentage of women who had an increase from baseline in endometrial thickness of greater than 4 mm (20% for BZA/CE and 17% for placebo) or an increase of greater than 8 mm (2.2% for BZA/CE and 3.8%

for placebo) was also similar between the BZA/CE and placebo groups. No cases of endometrial hyperplasia were reported in the SMART-2 trial, and the SMART-3 trial showed no differences between the BZA 20-mg/CE 0.45- and 0.625-mg groups and the placebo group in the incidence of endometrial disorders (Table 2) [16•, 17•].

Breast Safety

In an ancillary, retrospective study of the SMART-1 trial, the effects of BZA 20 mg/CE 0.45 and 0.625 mg on mammographic breast density were evaluated in a subset of women who completed 2 years of therapy and had mammograms at baseline and year 2 ($n=507$). The change from baseline in breast density was similar among the BZA/CE and placebo groups at 2 years: the mean percent change ($\pm$ SE) from baseline was $-0.39\%\pm 1.75\%$ for BZA 20 mg/CE 0.45 mg; $-0.05\%\pm 1.68\%$ for BZA 20 mg/CE 0.625 mg; and $-0.42\%\pm 1.72\%$ for placebo (Table 2) [24]. Additionally, a pooled analysis of data for the BZA 20-mg/CE 0.45-mg and placebo groups from the SMART-1, SMART-2, and SMART-3 trials showed no differences between the two groups in the incidence of breast-related adverse events (AES; 0.6% for BZA 20 mg/CE 0.45 mg and 0.7% for placebo) [25]. BZA/CE treatment also did not increase the incidence of breast

Table 2 Summary of key safety/tolerability findings for BZA/CE

SMART-1	SMART-2	SMART-3
<i>Endometrial safety</i>		
<ul style="list-style-type: none"> • Low rates of endometrial hyperplasia (<1%) at 2 years for BZA 20 and 40 mg/CE 0.45 and 0.625 mg, similar to PBO [20••] • Minimal increases in endometrial thickness (<1 mm) at 2 years for BZA 20 and 40 mg/CE 0.45 and 0.625 mg, similar to PBO [20••] 	<ul style="list-style-type: none"> • No cases of endometrial hyperplasia in any group [16•] • No difference in mean change from baseline in endometrial thickness at 12 weeks among the BZA 20-mg/CE 0.45- and 0.625-mg and PBO groups [16•] 	<ul style="list-style-type: none"> • No difference in incidence of endometrial disorders among the BZA 20-mg/CE 0.45- and 0.625-mg and PBO groups [17•]
<i>Breast safety</i>		
<ul style="list-style-type: none"> • No difference in change from baseline in mammographic breast density at 2 years among the BZA 20-mg/CE 0.45- and 0.625-mg and PBO groups [24] • No increase in incidence of breast pain for BZA/CE groups compared with PBO [15••] 	<ul style="list-style-type: none"> • No increase in incidence of breast pain for BZA/CE groups compared with PBO [16•] 	<ul style="list-style-type: none"> • No increase in incidence of breast pain for BZA/CE groups compared with PBO [17•]
<i>Bleeding-related events</i>		
<ul style="list-style-type: none"> • High rates of cumulative amenorrhea at 2 years for BZA 20 and 40 mg/CE 0.45 and 0.625 mg, similar to PBO [18•] 	N/A	N/A
<i>Overall safety and tolerability</i>		
<ul style="list-style-type: none"> • No difference in overall incidence of AEs among BZA/CE and PBO groups [15••] • No increase in incidence of VTEs for BZA/CE groups compared with PBO [15••] 	<ul style="list-style-type: none"> • No difference in overall incidence of AEs among BZA/CE and PBO groups [16•] • No VTEs reported in any group [16•] 	<ul style="list-style-type: none"> • No difference in overall incidence of AEs among BZA/CE and PBO groups [17•]

BZA bazedoxifene, CE conjugated estrogens, SMART Selective estrogens, Menopause, And Response to Therapy, PBO placebo, N/A not available, AE adverse event, VTE venous thromboembolic event

pain compared with placebo across the three trials (Table 2) [15•, 16, 17•].

Bleeding-Related Events

The rate of cumulative amenorrhea, defined as the percentage of subjects who had no bleeding or spotting over consecutive 4-week cycles, was evaluated in the SMART-1 trial. BZA 20 and 40 mg/CE 0.45 and 0.625 mg were associated with high rates of cumulative amenorrhea (>83% during cycles 1–13 and >93% during cycles 10–13) over 1 year of treatment, similar to that observed with placebo [18•]. The high rates of cumulative amenorrhea for these BZA/CE doses were sustained over 2 years of treatment (Table 2) [26]. The BZA 20- and 40-mg/CE 0.45- and 0.625-mg groups also had a low incidence of bleeding or spotting events, similar to placebo. In contrast, BZA 10 mg/CE 0.45 and 0.625 mg showed slightly lower cumulative amenorrhea rates compared with placebo. There were no differences in the incidence of bleeding-related AEs for BZA 10 mg/CE 0.45 mg and BZA 20 and 40 mg/CE 0.45 and 0.625 mg compared with placebo. Consistent with this, a pooled analysis of data for the groups receiving BZA 20 mg/CE 0.45 mg or placebo from the SMART-1, SMART-2, and SMART-3 trials showed that the incidences of bleeding-related adverse events were low and similar among the two groups [25].

General Safety and Tolerability

Overall, there were no significant differences between the BZA/CE and placebo groups in the incidence of AEs or study discontinuations due to AEs across the SMART-1, SMART-2, and SMART-3 trials (Table 2) [15•, 16•, 17•, 25]. The incidence of treatment-emergent AEs (TEAEs) was similar among the BZA/CE and placebo groups (range, 90–94% vs 92% in SMART-1; 61–67% vs 73% in SMART-2; 75–80% vs 71% in SMART-3); most TEAEs were mild to moderate in severity. BZA/CE was not associated with greater incidences of cardiovascular AEs or venous thromboembolic events (VTEs) when compared with placebo [15•, 16•].

Metabolic Parameters

Lipid Parameters

In the SMART-1 trial, all BZA/CE groups had a decrease from baseline in total cholesterol at 24 months. This decrease was greater for all BZA/CE groups than for placebo, but the difference was statistically significant only for BZA 20 mg/CE 0.45 mg ($P<0.05$ vs placebo; Table 3). All BZA/CE doses also resulted in a significantly greater reduction from baseline in low-density lipoprotein (LDL) cholesterol

($P<0.01$) and a greater increase in high-density lipoprotein (HDL) cholesterol ($P<0.05$), compared with placebo [15•]. In the SMART-2 trial, BZA 20 mg/CE 0.45 and 0.625 mg showed significantly greater reductions from baseline in total and LDL cholesterol at 12 weeks compared with placebo ($P<0.05$) [16•]. Similarly, BZA 20 mg/CE 0.45 and 0.625 mg showed a significantly greater decrease from baseline in LDL cholesterol at 12 weeks compared with placebo ($P<0.01$) in the SMART-3 trial [17•].

There was a significantly greater increase from baseline in triglycerides for BZA 20 and 40 mg/CE 0.625 mg and BZA 20 mg/CE 0.45 mg compared with placebo ($P<0.05$) in the SMART-1 trial and for BZA 20 mg/CE 0.625 mg compared with placebo ($P<0.05$) in the SMART-3 trial (Table 3) [15•, 17•]. In the SMART-2 trial, the change in triglycerides from baseline was similar between the BZA/CE and placebo groups, but a higher proportion of women in the placebo group had increases in triglycerides that were deemed to be potentially clinically important (>3.7 mmol/L) compared with the BZA/CE groups [16•].

Coagulation Parameters

Coagulation factors were assessed in the SMART-1 trial [15•]. At 2 years, there was no effect of BZA/CE on serum concentrations of D-dimer. All BZA/CE doses resulted in decreases from baseline in PAI-1 antigen serum levels ($P<0.05$ for BZA 20 mg/CE 0.625 mg) and PAI-1 activity ($P<0.05$ for BZA 10 and 20 mg/CE 0.625 mg and BZA 40 mg/CE 0.45 mg). All BZA/CE groups also showed increases in plasminogen activity from baseline ($P<0.001$) and significantly greater decreases from baseline in fibrinogen levels, compared with placebo ($P<0.001$). The change from baseline in protein C activity was similar between the BZA/CE and placebo groups. All BZA/CE groups showed a significantly greater decrease from baseline in antithrombin III activity ($P<0.05$ vs placebo) and a significantly greater increase from baseline in protein S activity ($P<0.01$ vs placebo) compared with placebo.

Sleep and Quality of Life

The effects of BZA 20 mg/CE 0.45 and 0.625 mg on sleep and quality of life were evaluated in the SMART-2 trial in women who received at least one dose of their assigned study medication and had a baseline and at least one on-therapy measurement using the Medical Outcomes Study (MOS) sleep scale and Menopause-Specific Quality of Life (MENQOL) questionnaires. Both BZA/CE doses showed significantly greater improvement from baseline in sleep parameters including time to fall asleep, sleep disturbance, sleep adequacy, and sleep problems indexes I and II compared with placebo ($P<0.001$) at week 12 (Table 3)

Table 3 Effects of BZA/CE on metabolic parameters, sleep, and quality of life

SMART-1	SMART-2	SMART-3
<i>Metabolic parameters</i>		
<ul style="list-style-type: none"> Significant decrease from baseline in total cholesterol at 24 months for BZA 20 mg/CE 0.45 mg vs PBO ($P<0.05$) [15••] Significant decrease in LDL cholesterol and increase in HDL cholesterol from baseline at 24 months for BZA 10, 20, and 40 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [15••] Significant increase from baseline in triglycerides for BZA 20 mg/CE 0.45 and 0.625 mg and BZA 40 mg/CE 0.625 mg vs PBO ($P<0.05$) [15••] 	<ul style="list-style-type: none"> Significant decrease in total and LDL cholesterol from baseline at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [16•] 	<ul style="list-style-type: none"> Significant decrease in LDL cholesterol from baseline at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.01$) [17•] Significant increase from baseline in triglycerides for BZA 20 mg/CE 0.625 mg vs PBO ($P<0.05$) [17•]
<i>Sleep and quality of life</i>		
N/A	<ul style="list-style-type: none"> Significant improvement in sleep parameters at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.001$) [21] Significant improvement in total and vasomotor function MENQOL scores at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.001$) [21] Significantly greater satisfaction with treatment at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [21] 	<ul style="list-style-type: none"> Significant improvement in total, vasomotor function, and sexual function MENQOL scores at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [22] Significantly greater satisfaction with treatment at 12 weeks for BZA 20 mg/CE 0.45 and 0.625 mg vs PBO ($P<0.05$) [22]

BZA bazedoxifene, CE conjugated estrogens, SMART Selective estrogens, Menopause, And Response to Therapy, PBO placebo, LDL low-density lipoprotein, HDL high-density lipoprotein, N/A not available, MENQOL Menopause-Specific Quality of Life

[21]. Significantly greater improvement in sleep quantity was also seen for BZA 20 mg/CE 0.625 mg at 12 weeks compared with placebo ($P\leq 0.01$). Regression analysis showed a significant association ($P<0.05$) between improvements in sleep parameters and reductions in moderate to severe hot flashes seen with BZA/CE. Both BZA/CE groups showed significantly greater improvement in vasomotor function and total MENQOL scores at 12 weeks compared with placebo ($P<0.001$; Table 3). The BZA/CE groups also had significantly higher percentages of women who reported overall satisfaction with treatment on the Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) compared with placebo (73.5% and 78.2% for BZA 20 mg/CE 0.45 and 0.625 mg, respectively, versus 44.4% for placebo; $P<0.001$ for both vs placebo).

In the SMART-3 trial, the effects of BZA/CE on sexual function, quality of life, and satisfaction with treatment were evaluated using the Arizona Sexual Experiences (ASEX) scale, the MENQOL questionnaire, and the MS-TSQ [22]. The data were analyzed for all women who were randomized, received at least one dose of their assigned study medication, and had a baseline and at least one on-therapy measurement. The BZA 20-mg/CE 0.45- and 0.625-mg groups showed significantly greater improvement in ease of lubrication at 12 weeks compared with placebo ($P<$

0.05), as measured on the ASEX scale. Both BZA/CE doses also resulted in significantly greater improvement in vasomotor function, sexual function, and total scores on the MENQOL questionnaire compared with placebo or BZA 20 mg alone at week 12 ($P<0.05$; Table 3). A significantly greater proportion of BZA/CE-treated women reported overall satisfaction with treatment on the MS-TSQ, compared with those who received placebo or BZA 20 mg: 62.6% and 69.4% for BZA 20 mg/CE 0.45 and 0.625 mg, respectively, versus 40.4% for BZA 20 mg ($P<0.001$) and 47.4% for placebo ($P<0.05$). BZA/CE-treated women were also more satisfied than those in the placebo and BZA 20-mg groups with the ability to control hot flashes during the day and at night ($P<0.001$ for both), the effect on quality of sleep ($P<0.001$), and the effect on mood or emotions ($P<0.05$).

Conclusions

TSECs such as BZA/CE have the potential to provide the favorable effects of estrogens on menopausal symptoms and bone with the protective effects of a SERM on the uterus and breast. In the SMART trials, BZA 20 mg/CE 0.45 and 0.625 mg were shown to be effective in treating menopausal symptoms, including VMS and symptoms of VVA, and in

preserving bone mass in postmenopausal women. These BZA/CE doses were associated with a favorable safety and tolerability profile over 2 years of treatment, including high rates of cumulative amenorrhea and positive effects on the lipid profile, and showed no evidence of endometrial or breast stimulation. BZA/CE-treated women reported significantly improved quality of life and satisfaction with treatment. Thus, BZA/CE may be a promising option for postmenopausal women seeking a comprehensive therapy to treat menopausal symptoms and prevent osteoporosis. The observation in the SMART trials that different doses of BZA/CE have different clinical responses indicates that the ratio of BZA to CE affects the efficacy and safety of the BZA/CE complex. An important consideration for the development of future TSECs will therefore be a careful determination of the optimal ratio of SERM to estrogen(s) to maximize clinical benefit while ensuring safety.

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