Profile of bazedoxifene/conjugated estrogens for the treatment of estrogen deficiency symptoms and osteoporosis in women at risk of fracture

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Abstract: Decreasing levels of estrogens during menopause are associated with reduced bone density and an increased risk of osteoporosis. Many women also experience bothersome vasomotor and vaginal symptoms during the menopausal transition. Results of systematic reviews and meta-analyses of randomized controlled trials have shown that both systemic estrogen therapy or hormone therapy (estrogen combined with a progestin) are useful to prevent bone loss, and they are the most effective treatment for such climacteric symptoms as hot flushes, sweating, vaginal dryness, and dyspareunia. Unfortunately, estrogen therapy and hormone therapy increase the risk of endometrial and breast cancer, respectively. The selective estrogen receptor modulators (SERMs) result in positive estrogenic effects on bone, with no negative effects on the endometrium and breast but do not provide relief from postmenopausal symptoms. The combination of a SERM with estrogen as a tissue selective estrogen complex (TSEC) is a new strategy for the prevention of bone loss and the treatment of climacteric symptoms. This combination is particularly interesting from a clinical point of view, taking into account that estrogen alone did not increase breast cancer risk by the Women’s Health Initiative. TSEC is hypothesized to provide the benefits of estrogen-alone therapy, with an improved tolerability profile because the SERM component can make possible the elimination of progestin. The objective of this review was to critically evaluate the evidence from the reports published to date on the use of bazedoxifene (a third-generation SERM) in combination with conjugated estrogens in postmenopausal women. The conclusion is that effectively, the combination of bazedoxifene and conjugated estrogens may be a promising alternative to hormone therapy for the prevention of osteoporosis and the treatment of postmenopausal symptoms in non-hysterectomized postmenopausal women.

Keywords: tissue selective estrogen complex, menopause, bone mineral density, bone turnover markers, climacteric symptoms

Introduction

Notable is the increased risk of osteoporosis, cardiovascular disease, and vasomotor instability observed in women, subsequent to the cessation of ovarian estrogen production that occurs at menopause.1,2 Climacteric symptoms, such as hot flushes (HFs) or sweating, and vulvar and vaginal atrophy (VVA) are common complaints in postmenopausal women.3–6 Bone loss, although asymptomatic, can be relevant, especially in their early postmenopausal years.7,9 It is not surprising, therefore, that estrogen therapy (ET) (estrogen alone) or hormone therapy (HT) (estrogen combined with a progestin) are among the most effective therapies for the treatment and prevention of osteoporosis.7 Both regimens normalize bone remodeling and, unlike other antiresorptive therapies, such as bisphosphonates, their use is not associated with...
increased risk of atypical femoral fractures or osteonecrosis of the jaw.\textsuperscript{10–12} However, while the beneficial effects of ET/HT in bone are unquestioned, the increased risk of breast cancer, cardiovascular disease, and dementia observed in elderly women participating in the Women’s Health Initiative (WHI) study, have resulted in a dramatic decrease in the use of estrogen treatment in the climacteric patient and in postmenopausal women at high risk for osteoporosis.\textsuperscript{13,14}

Regardless, it is clear that the estrogen receptor (ER) and its signaling pathways are extremely useful targets in bone, and it is anticipated that compounds that modulate this axis, and exhibit a more favorable therapeutic index, will have considerable clinical utility. The selective estrogen receptor modulators (SERMs), a class of compounds whose relative ER-agonist/antagonist activity can differ between target organs, are a first step in this direction. An “ideal” SERM would act as an ER agonist by having a protective effect on bone and improving lipid parameters, while also acting as an ER antagonist by maintaining breast and endometrial safety.\textsuperscript{15} In this way, the treatment could result in positive estrogenic effects on bone and lipid metabolism, with no negative effects on the endometrium and breast.

SERMs are useful for the prevention and treatment of postmenopausal osteoporosis, but unfortunately, they do not provide relief from climacteric symptoms.\textsuperscript{16,17}

A new strategy is the combination of a SERM with estrogen(s), described as a tissue selective estrogen complex (TSEC), based on the simultaneous but differential effects of each compound on estrogen receptor activity.\textsuperscript{18–24}

In this review, we critically evaluate the evidence from the reports published to date on the use of bazedoxifene (BZA) (a third-generation SERM) in combination with conjugated estrogens (CE) in postmenopausal women. PubMed was searched from inception to February 2013, using the key words bazedoxifene and conjugated estrogens.

**Bazedoxifene (bazedoxifene acetate)**

BZA is a novel SERM developed for the prevention and treatment of postmenopausal osteoporosis. It is a new molecule with unique structural characteristics compared with raloxifene and tamoxifen, two other compounds referred to as SERMs.\textsuperscript{20} Its molecule was developed based on the raloxifene model, replacing the benzothiophene core with an indole ring.\textsuperscript{20,25} BZA can interact with ERs alpha and beta in bone, breast, uterus, blood vessels, and liver; the binding affinity is slightly greater for ER-alpha versus ER-beta. The average half-life is 28 hours and maximum concentration is reached in 1–2 hours after oral administration; it is mainly excreted by feces (84.7%), while renal excretion is negligible.\textsuperscript{26,27} The main metabolic pathway is glucurono-conjugation; its metabolism is poorly mediated by cytochrome P450, and as a consequence, BZA has a low risk of pharmacological interactions.\textsuperscript{27}

In animal models, BZA treatment was shown to maintain or increase bone mineral density (BMD), preserve normal histological bone quality, improve bone compressive strength, and reduce total cholesterol levels.\textsuperscript{28} The evidence shown in the animal model has also been confirmed in the human. In fact, in a Phase II, randomized, double-blind, controlled study of healthy postmenopausal women, BZA (up to 40 mg daily dose) did not stimulate the endometrium, nor increase the incidence of breast pain and induced a significant reduction in markers of bone remodeling.\textsuperscript{29–31}

Clinically, BZA has been evaluated in two global, randomized, double-blind, placebo- and active-controlled, Phase III studies: an osteoporosis prevention study and an osteoporosis treatment study.\textsuperscript{32,33}

The osteoporosis prevention study was a large 24-month, randomized, double-blind clinical trial involving 1,434 healthy postmenopausal women (mean age, 58 years; mean time from last menstrual period, 11 years) with a BMD T-score at the lumbar spine or femoral neck below −1.0 and −2.5 or clinical risk factors for osteoporosis. This study compared the efficacy and safety of three doses of daily BZA (10, 20, or 40 mg) with placebo and raloxifene (60 mg daily) in the prevention of postmenopausal osteoporosis.\textsuperscript{32} All doses of BZA and raloxifene prevented lumbar and femoral bone loss, while in the placebo group, a significant loss in BMD was found. All active groups showed significant differences in comparison with the placebo group ($P < 0.001$), in terms of BMD changes. A significant decrease in osteocalcin and C-telopeptide plasma levels versus the baseline and placebo group level was observed in all active-treatment groups, from the third month of observation and throughout the study ($P < 0.001$). The study showed that the treatment with BZA prevented the postmenopausal bone loss and reduced bone turnover markers (BTM) equally as well as raloxifene and was generally well tolerated, without stimulating the endometrium.\textsuperscript{34}

The osteoporosis treatment study was a registrative international, multicenter, double-blind, randomized, placebo- and active-controlled Phase III trial conducted at 206 sites worldwide. It was performed to evaluate the safety and efficacy of BZA in treating postmenopausal women with osteoporosis.\textsuperscript{33} This trial used an active comparator (raloxifene), in addition to placebo and involved 7,492 women.
(55–85 years of age) with radiographically confirmed vertebral fractures (about 56% of study population) or with lumbar spine or femoral neck BMD T-scores between −2.5 and −4.0. The primary endpoint was the incidence of new radiographically confirmed vertebral fractures after 3 years. Secondary endpoints included incidence of nonvertebral fractures, changes from baseline in BMD of the lumbar spine and total hip, and changes in biochemical markers of bone resorption and bone formation. In the intent-to-treat analysis, the incidence of new vertebral fractures was significantly lower (P < 0.05) in all active-treatment groups versus the placebo group, with relative risk reductions of 42%, 37%, and 42%, respectively, in patients treated with BZA 20 mg, BZA 40 mg, and raloxifene 60 mg.33 No significant differences were found in the incidence of nonvertebral osteoporosis–related fractures among treatment groups, but in a post hoc analysis of a subgroup of women (n = 1,772) at higher risk of fracture (femoral neck T-score < −3.0 and/or more than one moderate or severe vertebral fracture or multiple mild vertebral fractures), BZA 20 mg showed a 50% and 44% reduction in nonvertebral fracture risk relative to placebo (P < 0.02) and raloxifene 60 mg (P < 0.05) respectively. When the data for both BZA treatment groups were combined, the incidence of nonvertebral fractures was 40% lower compared with placebo (P = 0.03).33 The osteoporosis treatment study also confirmed positive data on the surrogate markers of fracture’s risk: BMD and the BTMs.

Further data from subsequent 5-year (4,216 women) and 7-year (1,732 women) extensions of the 3-year study have confirmed anti-fracture efficacy at the vertebral level with BZA 20 mg/day, with a relative risk reduction of 30% in comparison with placebo (P < 0.022).35,36 BZA was generally well tolerated, both in the osteoporosis prevention and treatment study: the overall incidence of adverse events, serious adverse events, and adverse events leading to treatment interruption, in the BZA-treated groups was not different from placebo.32,33 Nevertheless, in the prevention study, the incidence of HFIs in the BZA groups (20%–24%) and the raloxifene group (19%) was higher than that in the placebo group (14%) (overall P < 0.05).32 Also during the osteoporosis treatment study, the incidence of HFIs and leg cramps was similar among the bazedoxifene and raloxifene treatment groups (12.6% vs 12.0% and 10.9% vs 11.7%, respectively), but significantly higher than that reported with placebo (6.3% and 8.2%, respectively).33 However, another study evaluated BZA’s role in inducing HFIs in postmenopausal women, in comparison with placebo, during a 12-weeks period of observation; results showed that BZA did not increase the incidence, number, or intensity of hot flushes compared with placebo, in postmenopausal women not suffering from this symptom before the start of administration.37 The incidence of venous thromboembolism (VTE) was greater with BZA 20 mg/day compared with placebo, however low in absolute terms (BZA 20 mg/day: 2.8 cases per 1,000 women-year; placebo: 1.7 cases per 1,000 women-year).32,33

Bazedoxifene/conjugated estrogens Rationale

The known antimitotic activity of BZA in the uterus and endometrium offers the possibility to associate this SERM to an estrogen, in the form of a CE, to form an association currently called a TSEC, so as to control menopausal syndrome (hot flushes, sweating, vaginal dryness, bone loss, etc) in postmenopausal women.21,22 In this way, a SERM, like BZA, can protect the endometrium from the proliferative action exerted by an estrogen, and this fact allows us to use estrogen without progestin in postmenopausal women, taking into account that estrogen alone does not increase breast cancer risk in postmenopausal women, as demonstrated in the estrogen-only arm of the WHI.38 Moreover the association of BZA with CE might protect the skeleton from bone loss, in postmenopausal women.

Preclinical studies

Preclinical studies have shown different responses to various SERMs when combined with CE.

In ovariectomized rats, BZA/CE increased BMD and volume, without alterations in bone histology.22 Moreover, animal studies have shown different responses of estrogen tissues to various SERMs when combined with CE. BZA was the most potent SERM in inhibiting CE-induced increases in uterine wet weight, and the mammary gland stimulation in response to CE was inhibited to the greatest extent with BZA versus raloxifene or lasofoxifene.23

Clinical studies

The Phase II clinical trial of BZA/CE included 412 healthy postmenopausal women; the findings were that several doses of BZA/CE diminished the frequency and severity of hot flushes and reduced bone resorption, without stimulation of the endometrium or breast.39

The results from four Phase III studies, known as the Selective estrogens, Menopause, And Response to Therapy (SMART) trials, were recently reported in several publications.40-46 The design of the SMART trials, including participant inclusion criteria, is summarized in Table 1.
Safety and tolerability were also reported for each of the SMART trials.\textsuperscript{41,42,44–46}

### Effects on BMD and BTMs

The efficacy of BZA/CE in preventing bone loss was evaluated by changes in BMD, as measured by dual-energy X-ray absorptiometry; changes in BTMs, as surrogate markers of bone formation and bone resorption, were also assessed. Although there has been some variability associated with BTMs measurement, these markers are widely used to evaluate bone metabolism and treatment response to bone-active therapies.

#### BMD

In both sub-studies of the SMART-1 study, an increase in BMD at the lumbar spine, from baseline to 12 and 24 months, was observed in postmenopausal women treated with BZA/CE; this was significantly different ($P < 0.001$) from the decrease in BMD observed with placebo.\textsuperscript{43} The adjusted annual percent changes in lumbar spine BMD from baseline in women \textgreater{} 5 years postmenopause are shown in Figure 1. The BMD increases seen in women taking higher BZA doses (combined with CE) were smaller than those in women taking lower BZA doses, probably based on the simultaneous but differential effects of each compound on estrogen receptor activity.

However, compared with raloxifene, mean changes in BMD in the lumbar spine at month 24 were significantly greater for all BZA/CE doses, except for 40 mg BZA, in women 1 to 5 years postmenopause, which was similar to raloxifene.\textsuperscript{43}

Similar significant results for total hip BMD were also observed for all BZA/CE doses versus placebo ($P < 0.01$)
at months 12 and 24 in both groups of women.\textsuperscript{43} Generally, mean percentage increases in BMD at 12 and 24 months were also significant ($P < 0.05$) compared with placebo, at the femoral subregions (intertrochanteric, neck, and trochanteric regions), for all BZA/CE doses.\textsuperscript{43}

**BTMs**

The median percentage changes from baseline in the BTMs osteocalcin and C-telopeptide were also significantly greater with all BZA/CE doses versus placebo ($P < 0.001$) and most with BZA/CE doses versus raloxifene ($P < 0.05$) (Figure 2).\textsuperscript{43}

**Effects on estrogen deficiency symptoms**

Postmenopausal women may experience a variety of symptoms associated with a decline in the level of estrogens. Vasomotor symptoms, such as HFs, are reported by 60%–85% of women during menopause. Symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia, and increases in urinary frequency, urgency, or incontinence) are reported by 50% of postmenopausal women.
HFs
The efficacy of BZA/CE on vasomotor symptoms was evaluated by measuring the frequency and severity of HFs in response to treatment.

In the SMART-1 study, HFs were evaluated in 261 women with at least seven moderate-to-severe HFs per day or 50 per week.\textsuperscript{48} Compared with placebo, all BZA/CE doses significantly reduced the daily number of HFs at most time points and HF severity at week 12, except for BZA/CE doses containing BZA 40 mg.\textsuperscript{49}

The SMART-2 study examined HFs as a primary endpoint.\textsuperscript{44} At weeks 4 and 12, women taking BZA/CE had significant reductions from baseline in the mean daily number and severity of moderate-to-severe HFs compared with placebo.\textsuperscript{44} The number of HFs was reduced by 74% and 80% with BZA 20 mg/CE 0.45 and 0.625 mg, respectively, versus 51% with placebo (Figure 3).\textsuperscript{44} Significant decreases in HF frequency and severity with both BZA/CE doses compared with placebo were seen as early as week 2 or 3.\textsuperscript{41,44}

VVA
Changes in the proportion of vaginal superficial, parabasal, and intermediate cells improved, showing increased numbers of superficial cells (an estrogen-like effect on the vaginal surface) in women using BZA 10 or 20 mg/CE 0.625 or 0.45 mg in the SMART-1 trial.\textsuperscript{45} VVA was also assessed using four coprimary endpoints, in 664 postmenopausal women taking BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, BZA 20 mg, or placebo, in the SMART-3 trial.\textsuperscript{45}

Similar results were reported at week 12 with both BZA/CE doses compared with placebo and BZA alone. Superficial cell increases with CE 0.625 mg alone have previously been reported, by approximately 20% after about 1 year of observation.\textsuperscript{47} Even if direct comparison between these studies cannot be made based on time-point differences, the increase was approximately 6% with BZA 20 mg/CE 0.625 mg at 12 weeks.\textsuperscript{45}

It is known that low estrogen levels induce a reduction in the glycogen content of the vaginal epithelium, which leads to inhibition of lactic acid production in the vagina and an increase in vaginal pH. Vaginal pH changes significantly improved with BZA 20 mg/CE 0.625 mg versus placebo and for both BZA/CE doses versus BZA alone.

About 70% of women with vaginal dryness and dyspareunia do not voluntarily mention this symptom to their general practitioner, even though they suffer from decreased quality of life as a result of these conditions. Improvements in the severity of the most bothersome VVA symptoms (vaginal dryness for example) were found for BZA 20 mg/CE 0.625 mg compared with placebo and for both BZA/CE doses compared with BZA alone.

Sleep, quality of life, satisfaction
Sleep disruptions, including increased time to fall asleep, nighttime awakenings, and daytime tiredness are common among postmenopausal women. Moreover, during menopause, many women experience bothersome symptoms, such as mood disturbances or sexual dysfunction, which may negatively impact quality of life.

Significant improvements, from the SMART trials, in terms of sleep, quality of life, and satisfaction in women treated with BZA/CE compared with placebo, are summarized in Table 2.\textsuperscript{48–51}

In the SMART-1 trial, women treated with BZA 20 mg/CE 0.45 and 0.625 mg had significant reductions in mean number of minutes to fall asleep, increases in mean minutes slept, and increases in quality of sleep score compared with placebo.\textsuperscript{48}

In the SMART-2 trial, BZA 20 mg/CE 0.45 and 0.625 mg significantly improved time to fall asleep, sleep disturbance, sleep adequacy, and overall sleep problems compared with placebo (\(P < 0.001\) for all), as assessed on the Medical Outcomes Study sleep scale.\textsuperscript{49}

In the SMART-1 trial, BZA 20 mg/CE 0.45 and 0.625 mg significantly improved total and vasomotor function Menopause-specific Quality Of Life (MENQOL) scores compared with placebo (\(P < 0.001\)).\textsuperscript{50} Similar results were observed in the SMART-2 trial.\textsuperscript{49,50}

In the SMART-3 trial, women treated with BZA 20 mg/CE 0.45 and 0.625 mg reported significant improvements in ease of lubrication on the Arizona Sexual
Table 2 Significant improvements from SMART trials, in terms of sleep, quality of life, and satisfaction, in women treated with BZA/CE compared with placebo48–51

| SMART-1 | · Reductions in mean number of minutes to fall asleep, increases in mean minutes slept, and increases in quality of sleep scores  
| SMART-2 | · Improved total and vasomotor function of the Menopause-specific Quality of Life (MENQOL) scores  
| SMART-3 | · Improved time to fall asleep, sleep disturbance, sleep adequacy, and overall sleep problems, as assessed on the Study sleep scale  

Abbreviations: BZA, bazedoxifene; CE, conjugated estrogens; SMART, Selective estrogens, Menopause, and Response to Therapy.

Experiences scale compared with placebo. Moreover, BZA 20 mg/CE 0.45 and 0.625 mg were associated with significant improvements from baseline in the total, vasomotor, and sexual function scores compared with placebo (P < 0.001 for all).51

In the SMART-2 trial, the Menopause Symptoms Treatment Satisfaction Questionnaire results showed that 73.5% of women treated with BZA 20 mg/CE 0.45 mg and 78.2% of women treated with BZA 20 mg/CE 0.625 mg were satisfied with treatment compared with 44.4% of women given placebo (P < 0.001).49 Similar results were observed in the SMART-3 trial.51

Safety
In all the SMART trials, the overall incidence of adverse events (AEs) was similar between women in the BZA/CE and placebo groups, without significant difference in the number of patients discontinuing because of AEs.41,44,45

In the SMART-1 trial, the largest and longest SMART trial, the incidence of VTE or cardiovascular events was low and similar for women treated with BZA/CE or placebo.41 No VTEs were reported in the SMART-2 or SMART-3 trials, but these studies were of 12-week duration.44,45

However, the SMART trials were not powered to determine between-group differences in VTE or cardiovascular events.

In terms of laboratory findings, it is known that women may experience adverse changes in metabolic profile during the menopausal transition, including increases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and decreases in high-density lipoprotein (HDL) cholesterol.52 The long-term effects of BZA/CE on lipid parameters were evaluated in the SMART-1 trial.41 At Month 24, BZA 20 mg/CE 0.45 and 0.625 mg were associated with decreases from baseline in total cholesterol (for BZA 20 mg/CE 0.45 mg versus placebo [P < 0.05]) and LDL cholesterol (for both doses vs placebo [P < 0.01]). HDL cholesterol increased from baseline vs placebo (P < 0.01) with BZA 20 mg/CE 0.45 and 0.625 mg, as did triglycerides (P < 0.01). These effects on serum lipids and lipoproteins are similar to that described with CE, but not with transdermal estrogen administration.53 Changes in coagulation factors, such as increases in levels of the coagulation protein factor VII and fibrinogen, have been shown to occur during the menopausal transition.52 Significant decreases from baseline in levels of fibrinogen, protein S activity, and anti-thrombin III activity were reported for BZA 20 mg/CE in the SMART-1 trial.41

After 12 months of therapy, no endometrial hyperplasia was observed for BZA 20 or 40 mg/CE 0.45 mg, BZA 40 mg/CE 0.625 mg, raloxifene, or placebo, and this did not increase after 24 months.40 To the contrary, the 10 mg BZA dose did not prevent the estrogen dose-dependent endometrial hyperplasia when coupled with CE 0.45 or 0.625 mg.40

A low incidence of bleeding or spotting was also seen in women using BZA 20 or 40 mg/CE 0.625 or 0.45 mg and was statistically similar to the results with placebo. In the recent SMART-4 study, BZA 20 mg/CE 0.45 and 0.625 mg significantly improved BMD while maintaining endometrial safety and showed a favorable safety/tolerability profile over 1 year.46

No significant differences in the occurrence of breast pain were found between BZA/CE, raloxifene, or placebo groups at any time interval.41,44,45

Conclusion
The results of systematic reviews and meta-analyses of randomized, controlled trials have shown that both systemic ET and HT are useful to prevent bone loss, and they are the most effective treatment for such climacteric symptoms as hot flushes, sweating, vaginal dryness, and dyspareunia. In women who have such symptoms, this treatment results in a
75% reduction in frequency and an 87% reduction in severity of the symptoms, relative to treatment with a placebo.\textsuperscript{54} Unfortunately, ET and HT increase the risk of endometrial and breast cancer, respectively.\textsuperscript{55,56}

BZA is a third-generation SERM that was developed on the raloxifene model, replacing its benzothiophene core with an indole ring. The results of Phase III studies of postmenopausal women at risk of osteoporosis (prevention study)\textsuperscript{32} and with osteoporosis (treatment study)\textsuperscript{33} demonstrate the efficacy of BZA in the prevention of postmenopausal bone loss and of vertebral fractures. Nevertheless, an increased incidence of HFs is common with SERMs administration, even if BZA did not increase HFs in comparison with placebo in postmenopausal women not suffering from this symptom at baseline.\textsuperscript{37}

This comprehensive review reports the clinical outcomes of randomized, double-blind, placebo-controlled Phase III trials using BZA/CE in postmenopausal women, supporting its use as a new menopausal therapy. BZA/CE therapy in postmenopausal women reduced the frequency and severity of HFs, improved symptoms of VVA, and prevented the loss of bone mass independently of years since menopause. Women taking various doses of BZA/CE might maintain or gain bone mass similarly to women taking currently approved CE/medroxyprogesterone acetate therapies.\textsuperscript{57} The increase in BMD with BZA/CE previously shown was due to the decrease in bone remodeling, as demonstrated by the significant decrease in serum BTMs, for all BZA/CE doses compared with the placebo group. Furthermore, serum levels of C-telopeptide for women treated with BZA/CE were reduced to the levels of premenopausal women.\textsuperscript{58} Reductions in BTMs are regarded as valid surrogate endpoints for anti-fracture efficacy. A relationship between reductions in BTMs and fracture incidence has also been reported: as BTMs decrease, fracture incidence decreases. A reduction of 30% in BTMs is sufficient to cause a significant decrease in vertebral fracture risk; the decrease has to be over 50% to have an effect on nonvertebral fracture incidence linked to effects on cortical bone, less responsive to treatment.\textsuperscript{59–61} The combination of 20 mg of BZA with 0.625 mg of CE achieves these results.

It was observed that adding incrementally higher doses of BZA to CE slightly diminished the effects of CE on BMD, BTMs, and HFs. Also, the data on endometrial safety show that doses containing 20 mg BZA have the most appropriate profile for postmenopausal women. Adding BZA to CE provides an alternative treatment for postmenopausal women that protects the endometrium, without the addition of a progestin. However despite current studies showing no increased risk for endometrial hyperplasia, breast cancer, or thromboembolic events, further studies evaluating a greater number of women for longer study periods will be needed to more accurately assess the risk for such AEs in women using such combination therapy.

In conclusion, BZA/CE may be a valid alternative to HT for the treatment of postmenopausal symptoms and prevention of osteoporosis in non-hysterectomized postmenopausal women. Thereby, the treatment target will not only be the osteoporosis, but also the whole menopausal syndrome. The results of the WHI study led to a drastic reduction of the use of ET and hormone replacement therapy for the prevention of osteoporosis, since the risk of breast and endometrial cancer seemed to outweigh the benefits. The combination of BZA/CE might extend the pharmacological prevention of osteoporosis to younger postmenopausal women for the lack of oncological risks and the symptomatic improvements. Therefore, this combination might improve the adherence to osteoporosis treatment in the clinical practice, often compromised by lack of motivation or safety concerns.\textsuperscript{62}

**Disclosure**

The authors declare no conflict of interests in this work.

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