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Menopause-specific quality of life across varying menopausal populations with conjugated estrogens/bazedoxifene

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ABSTRACT

Objective: Describe the effects of conjugated estrogens/bazedoxifene (CE/BZA), a new treatment for vasomotor symptoms (VMS) and osteoporosis prevention, on menopause-specific quality of life (MSQOL) across different patient population types in phase 3 clinical trials.
Design: MSQOL was prospectively evaluated in 4 randomized, double-blind, placebo-controlled studies. The populations studied included healthy, non-hysterectomized postmenopausal women with symptomatic VMS or vulvar–vaginal atrophy (VVA) and general postmenopausal women (eligible regardless of symptoms). Menopause-specific Quality of Life (MENQOL) questionnaire total and domain scores for CE 0.625 mg/BZA 20 mg and CE 0.45 mg/BZA 20 mg were evaluated and compared with established thresholds for clinically important differences (CID).
Results: Significant improvements compared with placebo were found with both CE/BZA doses in MENQOL vasomotor domain (−0.61 to −2.23 over 3–24 months) and total scores (−0.24 to −0.94) in the general and symptomatic VMS/VVA populations. Significant improvement compared with placebo in sexual domain (−0.11 to −0.72) was observed with the higher dosage for all populations, and with the lower dosage in the VVA (−0.71 at month 3) and general populations (−0.4 at months 12 and 24). Improvements in vasomotor domain exceeded the CID with both doses in symptomatic VMS populations and with the higher dosage in women with symptomatic VVA; for total MENQOL, the CID was exceeded with the higher dose in symptomatic VMS populations.
Conclusions: CE/BZA significantly improved overall and vasomotor-related MSQOL across populations of postmenopausal women with varying baseline symptom statuses. Women with greater menopausal symptoms at baseline were more likely to experience clinically meaningful changes.

1. Introduction

Menopause is a normal physiological process that is characterized by the permanent cessation of menses in women as a result of reduced ovarian hormone secretion usually between the ages of 45 and 55 years [1]. During this period women can experience an array of symptoms including hot flashes, night sweats, sleep and mood disorders, impaired memory, lack of concentration, nervousness, depression, insomnia, bone and joint complaints, and reduction of bone mass [2]. Some women have severe symptoms that profoundly affect their personal and social functioning, and menopause-specific quality of life (MSQOL) [3].

The Menopause-Specific Quality of Life Questionnaire (MENQOL) was developed in 1996 and has been used in various clinic and ethnic populations. A 29-item questionnaire, the MENQOL aims to capture MSQOL in domains of vasomotor, physical, psychosocial, and sexual functioning [4]. Unlike some of the other menopausal health-related quality of life (HRQL) instruments, one of the strengths of the MENQOL is its ability to not only gauge the frequency of these menopausal symptoms but also capture the degree of disruption in the woman's life in the previous 30 days due to the menopausal symptoms [4].

Conjugated estrogens (CE) combined with the selective estrogen receptor modulator bazedoxifene (BZA), represents a new

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Table 1
SMART trial design.

Study (Clinicaltrials.gov Identifier)	*N*	Treatment groups	Active comparator	Key inclusion criteria	Treatment duration
SMART-1 (NCT00675688) [12]	3544	CE 0.45 mg/BZA 10 mg CE 0.45 mg/BZA 20 mg CE 0.45 mg/BZA 40 mg CE 0.625 mg/BZA 10 mg CE 0.625 mg/BZA 20 mg CE 0.625 mg/BZA 40 mg Placebo	Raloxifene 60 mg	Generally healthy, postmenopausal women (ages 40–75 years) with intact uterus	24 months
SMART-2 (NCT00675688) [6,14]	332	CE 0.45 mg/BZA 20 mg CE 0.625 mg/BZA 20 mg Placebo	NA	Postmenopausal women (ages 40–65 years) with ≥7 moderate to severe hot flushes per day (≥50 per week) at baseline and intact uterus	12 weeks
SMART-3 (NCT00238732) [7,15]	664	CE 0.45 mg/BZA 20 mg CE 0.625 mg/BZA 20 mg BZA 20 mg Placebo	BZA 20 mg	Postmenopausal women (ages 40–65 years) experiencing moderate to severe symptoms associated with VVA at baseline with intact uterus	12 weeks
SMART-5 (NCT00808132) [8,17]	1886	CE 0.45 mg/BZA 20 mg CE 0.625 mg/BZA 20 mg Placebo	CE 0.45 mg/MPA 1.5 mg BZA 20 mg	General postmenopausal women (ages 40–65 years) with intact uterus MSQOL evaluated in a subgroup experiencing bothersome VMS and sleep disturbances	12 months

n, number of subjects randomized.
Abbreviations: BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; NA, not applicable; SMART, Selective estrogens, Menopause, And Response to Therapy; VMS, vasomotor symptoms; VVA, vulvar/vaginal atrophy; MSQOL, menopause-specific quality of life.

treatment option in the management of menopausal health for postmenopausal women with a uterus. CE/BZA maintains the established benefits of estrogen therapy for relief of vasomotor symptoms (VMS), vulvar–vaginal atrophy (VVA), and prevention of osteoporosis, while preventing the stimulatory estrogenic effects on the uterus and estrogenic/progestogenic effects on breast tissue. CE/BZA showed significant improvements in tolerability compared with estrogen plus progesterone therapy, as measured by lower rates of uterine bleeding and breast pain. CE/BZA treatment had an effect on breast density similar to placebo [5].

The effect of CE/BZA on MSQOL was prospectively evaluated in the Selective estrogens, Menopause, And Response to Therapy (SMART[2]) trials using the MENQOL questionnaire. Prior publications have presented primary findings from these studies on relief of hot flashes [6] and vaginal atrophy [7], effects on sleep [8], prevention of bone loss [9], effect on breast density [10], and endometrial and breast safety [10,11].

The objective of this paper is to describe the effects of two doses of CE/BZA (CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg) on MSQOL across the different populations of healthy postmenopausal women enrolled in 4 of the individual SMART trials and to assess the clinical relevance of the results based on published clinically important differences (CID) for the MENQOL domains and total score.

2. Methods

2.1. CE/BZA SMART trials

CE/BZA was evaluated in a series of multicenter, randomized, double-blind, placebo-controlled, and active-controlled phase 3 trials known as the SMART trials, which have been previously published [6–8,12–17]. The current analysis reviews changes in total and domain scores on the MENQOL across each of 4 of these individual trials with different patient populations (Table 1). SMART-4 results were not included here because a different formulation of CE/BZA with 18% lower BZA bioavailability was used, which might have confounded the results, and because the MENQOL was not collected as an endpoint [16].

SMART trial designs and inclusion/exclusion criteria are described in detail in earlier publications [6–8,12–17] and in brief in Table 1. All of the trials included generally healthy postmenopausal women with a uterus. SMART-1 ($N = 3544$) was a 2-year multidose trial. SMART-2 ($N = 332$) was a 12-week trial that enrolled women who had at least 7 moderate or severe hot flushes per day or 50 per week at baseline. SMART-3 ($N = 664$) was a 12-week trial of women with moderate to severe symptoms of vulvar–vaginal atrophy. In SMART-5 ($N = 1886$), MSQOL was evaluated using MENQOL in a subpopulation of women with bothersome VMS and sleep disturbances ($n = 459$).

The SMART study protocols and amendments received institutional review board approval, and the studies were conducted to the guidelines outlined in the Declaration of Helsinki. Written informed consents were obtained from all subjects before initiation of any study procedures.

2.2. Assessments

MSQOL was assessed using the 29-item self-administered MENQOL scale [4,18] (Fig. 1). Scores were reported for vasomotor, physical, sexual, and psychosocial function domains, as well as MENQOL aggregated (total) score. When completing the scale, subjects first indicated "yes/no" if they experienced the symptom in the last month and if "yes," how bothered they were by it. The transformed response scale ranged from 1 to 8, where 1 = not experiencing the symptom in the previous month, 2 = experiencing the symptom but "not bothered," up to 8 = experiencing the symptom and "extremely bothered." Domain scores were calculated as the mean of its constituent items, with scores ranging from 1 to 8 (higher scores indicate greater bother). The aggregated score was calculated as the mean of the domain scores. CIDs were defined and published for the MENQOL based on the SMART-2 data [19], and the SMART-3 data [20]. The authors used widely accepted anchor-based methodology [21] to determine CIDs for both the domain and total scores (Table 2).

[2] The members of SMART are listed in Appendix section.

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