

DUAVEE™ (Conjugated Estrogens/Bazedoxifene)

PRODUCT DOSSIER

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Approved Prescribing Information on DUAVEE™ (conjugated estrogens/bazedoxifene) can be accessed via the following link: <http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>. In the event that this link does not work, please access the product's Approved Prescribing Information at www.pfizer.com.

This dossier regarding Conjugated Estrogens/Bazedoxifene (CE/BZA) includes information of an off-label nature. Pfizer does not suggest or recommend the use of CE/BZA in any manner other than that described in the Prescribing Information.

The purpose of this document is to provide the clinical and/or pharmacoeconomic information regarding DUAVEE™ that was requested; it is not intended to be used for any other purpose. This document contains relevant information for DUAVEE™, which may or may not be included in the U.S. Prescribing Information (USPI). Pfizer does not suggest or recommend the use of DUAVEE™ in any manner other than as described in the USPI.

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LIST OF ABBREVIATIONS

AMCP	Academy of Managed Care Pharmacy
ASEX	Arizona Sexual Experiences Scale
BMD	bone mineral density
BMI	body mass index
BZA	bazedoxifene
CBT	core body temperature
CE	conjugated estrogens
CI	confidence interval
CRL	Complete Response Letter
EPT	estrogen-progestin therapy
ER	estrogen receptors
ET	estrogen therapy
FDA	Food and Drug Administration
FMP	final menstrual period
FRAX	Fracture Risk Analysis
FSH	follicle stimulating hormone
HT	hormone therapy
LMP	last menstrual period
MDD	major depressive disorder
MENQOL	Menopause-specific Quality of Life
MOS	Medical Outcomes Study
MRS	Menopausal Rating Scale
MS-TSQ	Menopause Symptoms-Treatment Satisfaction Questionnaire
NHWS	National Health & Wellness Survey
QD	once daily
QOL	quality of life
SE	standard error
SERM	selective estrogen receptor modulator
SF-36	Short Form-36
SMART	Selective estrogens, Menopause, And Response to Therapy
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SSRS	Social Science Research Solutions
STRAW	Stages of Reproductive Aging Workshop
TSEC	tissue selective estrogen complex
UI	urinary incontinence
VMS	vasomotor symptoms
VTE	venous thromboembolism
VVA	Vulvar/vaginal atrophy
WHO	World Health Organization

YSM

years since menopause

1.0 EXECUTIVE SUMMARY: CLINICAL AND ECONOMIC VALUE

DUAVEE™ (conjugated estrogens [CE]/bazedoxifene [BZA]) is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause, and for the prevention of postmenopausal osteoporosis [1].

DUAVEE™ pairs CE, composed of multiple estrogens that are agonists of estrogen receptors (ER) α and β , with BZA, an estrogen agonist/antagonist that acts as an agonist in some estrogen-sensitive tissues and an antagonist in others (eg, uterus) [2]. The pairing of CE with BZA produces a composite effect that is specific to each target tissue [1].

The CE/BZA phase 3 trial program consists of 5 placebo-controlled, double-blind studies, as shown in **Table 1.1**. The Selective estrogens, Menopause, And Response to Therapy (**SMART**)-4 trial was considered a supportive trial for regulatory filings. While the **SMART-4** trial was being conducted, results of CE/BZA bioequivalence testing revealed that the bioavailability of 1 of the BZA formulations used in **SMART-4** was approximately 18% lower than that used in **SMART-1** [3]. Thus, only general safety analyses from the **SMART-4** trial will be discussed.

Table 1.1. CE/BZA Phase 3 Summary of Clinical Experience

Study	N	Treatment arms (mg)	Key endpoints
SMART-1: 303 [4-10]	3,397	<ul style="list-style-type: none"> • CE 0.45/BZA 10, 20, 40 • CE 0.625/BZA 10, 20, 40 • Raloxifene 60 (control) • Placebo (control) 	<ul style="list-style-type: none"> • Endometrial hyperplasia at 12 months • BMD at 24 months • VMS at 3 months • Vaginal maturation at 6 months • Breast density at 24 months
SMART-2: 305 [11-13]	318	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • Placebo (control) 	<ul style="list-style-type: none"> • VMS at 3 months
SMART-3: 306 [14,15]	652	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • BZA 20 (control) • Placebo (control) 	<ul style="list-style-type: none"> • VVA at 3 months
SMART-4: 304 [3]	1,061	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • CE 0.45/MPA 1.5 (control) • Placebo (control) 	<ul style="list-style-type: none"> • Endometrial hyperplasia at 12 months • BMD at 12 months
SMART-5: 3307 [16,17]	1,843	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • BZA 20 • CE 0.45/MPA 1.5 (control) • Placebo (control) 	<ul style="list-style-type: none"> • BMD (efficacy) at 12 months • Endometrial hyperplasia (safety) at 12 months • Breast density at 12 months

Secondary endpoints included cumulative amenorrhea (**SMART-1** and **SMART-5**) and breast pain (**SMART-1**, **SMART-2**, and **SMART-5**).

CE, conjugated estrogens; BZA, bazedoxifene; SMART, Selective estrogens, Menopause, And Response to Therapy; BMD, bone mineral density; VMS, vasomotor symptoms; VVA, vulvar/vaginal atrophy; MPA, medroxyprogesterone acetate.

This dossier includes information that is beyond the label of CE/BZA. Pfizer does not suggest or recommend the use of CE/BZA in any manner other than as described in the Prescribing Information approved by the US Food and Drug Administration (FDA).

1.1 Clinical Benefits

Efficacy and Effectiveness/Safety/Tolerability

DUAVEE™ (CE/BZA) is indicated in women with a uterus for the treatment of moderate to severe VMS associated with menopause, and for the prevention of postmenopausal osteoporosis [1].

CE/BZA is formulated as an oral tablet containing CE 0.45 mg and BZA 20 mg and is recommended for once-daily (QD) dosing [1].

The efficacy of CE/BZA as treatment for moderate to severe VMS associated with menopause was established in the **SMART-2** study of women with ≥ 7 moderate to severe hot flashes per day or ≥ 50 per week at screening [11]. CE/BZA significantly reduced the mean daily number and severity of hot flashes compared with placebo at Weeks 4 and 12 ($P < 0.001$).

The efficacy of CE/BZA for the prevention of postmenopausal osteoporosis was demonstrated in the **SMART-1** and **SMART-5** trials. In the **SMART-1** Osteoporosis Prevention I and II substudies of postmenopausal women with at least 1 risk factor for osteoporosis, CE/BZA significantly increased lumbar spine and total hip bone mineral density (BMD) from baseline through Month 24 compared with placebo ($P < 0.05$) [5]. Bone turnover markers significantly decreased with CE/BZA compared with placebo at all time points ($P < 0.001$). In the **SMART-5** study of women ≤ 5 years since last menstrual period (LMP) with 2 evaluable BMD scans at screening of the lumbar spine and total hip that differed by $< 5.0\%$ and $< 7.5\%$, respectively, CE/BZA significantly increased lumbar spine and total hip BMD and showed significantly greater decreases from baseline in serum bone turnover markers compared with placebo at 12 months ($P < 0.01$ for all).

Across the CE/BZA phase 3 program, CE/BZA was associated with significant improvements in sleep parameters and quality of life (QOL), and greater satisfaction with treatment compared with placebo [12,15,17].

Rates of endometrial hyperplasia were $< 1\%$ with CE/BZA over 2 years [4], which is consistent with the endometrial safety standard established by the FDA (endometrial hyperplasia rate $\leq 1\%$) [18]. Based on adverse event data from studies up to 2 years in duration, no increased risk of venous thromboembolism (VTE) or cardiovascular events was observed with CE/BZA compared with placebo [6]. CE/BZA demonstrated noninferiority to placebo for change from baseline at 1 year in mammographic breast density, and the incidence of breast pain/tenderness with CE/BZA was not significantly different from placebo and significantly lower than that observed with CE/medroxyprogesterone acetate (MPA; $P < 0.01$) [16]. CE/BZA demonstrated a vaginal bleeding profile that was not significantly different from placebo and significantly better than that observed with CE/MPA ($P < 0.001$).

Shortcomings of Current Treatment and the Unmet Medical Need That CE/BZA Addresses

Hormone therapy (HT) is considered the most effective treatment for VMS [19]; yet, professional organizations suggest that HT administration should be highly individualized with thorough consideration of the risks and benefits associated with treatment [19,20]. Because of tolerability issues associated with HT, such as breakthrough vaginal bleeding, breast pain, and increased breast density [19,21], a pharmacologic agent that effectively treats VMS with an improved tolerability profile is needed.

The major pharmacologic options for the prevention of osteoporosis are bisphosphonates, raloxifene, and HT [22]. However, each of these options is associated with specific tolerability and/or safety concerns [22]. Individualized pharmacologic treatment is critical for optimizing osteoporosis management [23].

CE/BZA may be an alternative to traditional HT for the treatment of VMS in nonhysterectomized, postmenopausal women [24] and may also provide a favorable new option to HT for the prevention of postmenopausal osteoporosis [25]. CE/BZA is progestin free and attenuates estrogenic activity in a tissue-selective manner [26].

1.2 Economic Benefits

A mathematical model was developed to estimate the burden of evaluative procedures in patients presenting with postmenopausal bleeding (PMB) 6 to 12 and 3 to 12 months after initiation of CE/MPA versus CE/BZA. The model is organized such that patients (treated with either CE/MPA or CE/BZA presenting with PMB 6 to 12 or 3 to 12 months of hormonal therapy) transit through the PMB evaluation pathway until either pathology is defined or until no additional evaluation procedures are performed [100]. PMB evaluation procedures are accumulated accordingly. Hormonal therapies (CE/MPA versus CE/BZA) are compared at both time periods (6 to 12 and 3 to 12 months) on the basis of procedure volume [100].

The number of treated women who develop PMB during the 2 time periods was estimated on the basis of prospective randomized trial data [100]. The volume of PMB-evaluative procedures, including transvaginal ultrasound (TVU), endometrial biopsy (with or without transvaginal ultrasound), dilation and curettage (D&C), hysteroscopy D&C, ultrasonography, and saline infusion sonohysterography (SIS) were estimated from published guidelines and a survey of 5 expert healthcare providers with ongoing, real-world experience treating patients for postmenopausal bleeding [100].

Based on this exploratory modeling exercise, using CE/MPA to treat moderate to very severe VMS is associated with approximately 63,000 (PMB 6 to 12 months) to 80,000 (PMB 3 to 12 months) evaluation procedures annually [100]. Under assumptions used in the model, this procedure burden may be reduced by 68% to 71% through the use of CE/BZA instead of CE/MPA [100].

The results from the model suggest that the use of CE/BZA rather than CE/MPA offers an opportunity to reduce the frequency, and therefore burden, of evaluative procedures for patient and providers.

1.3 Conclusions

In women with a uterus seeking treatment for moderate to severe VMS or who would also benefit from protection from bone loss, there is an underserved medical need for therapies that provide endometrial protection with improved tolerability compared with HT [24]. CE/BZA represents a novel approach to effectively treat menopausal symptoms and prevent bone loss while protecting the endometrium [24]. In randomized, double-blind, placebo-controlled phase 3 studies, CE 0.45 mg/BZA 20 mg significantly reduced the number and severity of hot flushes compared with placebo, as well as significantly improved lumbar spine and total hip BMD and significantly decreased bone turnover markers from baseline compared with placebo [5,6,11]. Results from the phase 3 clinical trial program also showed beneficial effects of CE/BZA on sleep and QOL, and greater satisfaction with treatment compared with placebo [12,15,17]. Rates of endometrial hyperplasia were <1% with CE/BZA [4], and there were no increased risks of VTEs or cardiovascular events with CE/BZA compared with placebo [6]. CE/BZA demonstrated noninferiority compared with placebo for change from baseline in mammographic breast density, and rates of breast pain/tenderness with CE/BZA were not significantly different from placebo and significantly lower than with CE/MPA [16]. In addition, the vaginal bleeding profile with CE/BZA was not significantly different from placebo and significantly better than that observed with CE/MPA. Taken together, CE/BZA may be an alternative to traditional HT for the treatment of VMS in nonhysterectomized, postmenopausal women and may also provide a favorable new option to HT for the prevention of postmenopausal osteoporosis.

2.0 PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 Product Description

Note: Information contained in this section is a summary of information contained in the full Prescribing Information for CE/BZA. For additional information, please refer to the full Prescribing Information available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>. In the event that this link does not work, please access the product's Approved Prescribing Information at www.pfizer.com.

Generic Name, Brand Name, and Therapeutic Class of Product

Generic name: Conjugated estrogens/bazedoxifene (CE/BZA)

Brand name: DUAVEE™

Therapeutic class: Not applicable

Dosage Forms, Strengths, and Package Sizes

CE/BZA is formulated as an oral tablet containing CE 0.45 mg with BZA 20 mg and is recommended for QD dosing. CE/BZA tablets will be supplied in quantities of 30 tablets, provided in two 15-count blister packages. A 7-count blister pack will also be available for samples [87]. CE/BZA tablets should be taken once daily, with or without food [1].

National Drug Code

NDC 0008-1123-12

American Hospital Formulary Service Classification

The American Hospital Formulary Service (AHFS) classification for CE/BZA is 68:00 Hormones and Synthetic Substitutes.

FDA-Approved, Off-Label, and Other Studied Indications

CE/BZA was approved by the US FDA on October 3, 2013 for the treatment of the following conditions in women with a uterus: moderate to severe VMS associated with menopause, and for the prevention of postmenopausal osteoporosis [1].

Clinical development programs for CE/BZA include, but are not limited to, the studies listed in **Table 2.1**. A comprehensive list of Pfizer studies can be found at www.clinicaltrials.gov.

Table 2.1. Phase 3 Clinical Development Program for CE/BZA

Study	ClinicalTrials.gov Identifier	Study Title
SMART-1	NCT00675688	A Double-Blind, Randomized, Placebo- and Active-Controlled Safety and Efficacy Study of Bazedoxifene/Conjugated Estrogens Combinations in Postmenopausal Women
SMART-2	NCT00234819	A Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Bazedoxifene/Conjugated Estrogen Combinations for Treatment of Vasomotor Symptoms Associated With Menopause
SMART-3	NCT00238732	A Double-Blind, Randomized, Placebo- and Active-Controlled Efficacy and Safety Study of Bazedoxifene/Conjugated Estrogens Combinations for Treatment of Moderate to Severe Vulvar/Vaginal Atrophy in Postmenopausal Women
SMART-4	NCT00242710	A Double-Blind, Randomized, Placebo- and Active-Controlled Efficacy and Safety Study of Bazedoxifene/Conjugated Estrogens Combinations for Prevention of Endometrial Hyperplasia and Prevention of Osteoporosis in Postmenopausal Women
SMART-5	NCT00808132	A Double-Blind, Randomized, Placebo- and Active-Controlled Efficacy and Safety Study of the Effects of Bazedoxifene/Conjugated Estrogens Combinations on Endometrial Hyperplasia and Prevention of Osteoporosis in Postmenopausal Women

CE/BZA, conjugated estrogens/bazedoxifene; SMART, Selective estrogens, Menopause, And Response to Therapy.

Clinical Pharmacology

CE/BZA pairs CE, which is composed of multiple estrogens that are agonists to ER α and β , with BZA, which has estrogen agonist activities in some estrogen-sensitive tissues and estrogen antagonist activities in others (eg, uterus). This pairing results in a composite effect that is specific for each target tissue [1]. The BZA component reduces the risk of endometrial hyperplasia associated with the CE component [1].

Pharmacokinetics/Pharmacodynamics

No pharmacodynamic studies have been conducted. For pharmacokinetics, please refer to the complete Prescribing Information for CE/BZA available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>.

Contraindications/Warnings and Precautions/Adverse Effects

Please refer to the complete Prescribing Information for CE/BZA available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>.

Interactions

Drug/Drug

No drug interaction trials were conducted with CE/BZA. For more information, please refer to the complete Prescribing Information for CE/BZA available at:

<http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>.

Drug/Food

No drug/food interaction trials were conducted with CE/BZA.

Drug/Disease

Please refer to the complete Prescribing Information for CE/BZA available at:

<http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>.

Dosing and Administration

Please refer to the complete Prescribing Information for CE/BZA available at:

<http://labeling.pfizer.com/ShowLabeling.aspx?id-1174> for dosing for the treatment of moderate to severe VMS and the prevention of postmenopausal osteoporosis.

Access

CE/BZA will be available in the US in the first quarter of 2014. Please refer to the complete Prescribing Information for CE/BZA available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>.

Co-Prescribed/Concomitant Therapies

As stated in the complete Prescribing Information for CE/BZA (available at <http://labeling.pfizer.com/ShowLabeling.aspx?id-1174>), women taking CE/BZA with an inadequate daily intake of calcium and/or vitamin D should be supplemented. Recommended daily calcium intake for postmenopausal women ranges from 1,000 to 1,500 mg/day, and recommended daily vitamin D intake ranges from 800 to 1,000 IU/day [22].

Comparison of CE/BZA With Primary Comparator Products

Vasomotor Symptoms

Table 2.2 summarizes the product characteristics of the estrogen-progestin therapy (EPT) formulations and non-HT based options (eg, paroxetine) that are approved for the treatment of VMS and may be considered comparators to CE/BZA. Because CE/BZA is indicated for women with an intact uterus, systemic estrogen-only formulations (which are not generally recommended for nonhysterectomized women [19]) would not be considered direct comparators to CE/BZA in this specific patient population. It is important to note that these comparisons are not based on head-to-head comparative trials, but rather provide comparisons based on each product's prescribing information.

Table 2.2. Comparison of CE/BZA With Key Agents Indicated for the Treatment of VMS

		Estrogen-progesterone therapy formulations							SSRI
	DUAVEE™ (CE/BZA) [1]	Prempro® (CE/ MPA tablets) [27]	Premphase® (CE/ MPA tablets) [27]	Activella® (estradiol/norethindro ne acetate tablets) [28]	Angeliq® (drospirenone/ estradiol tablets) [29]	femhrt® (norethindrone acetate/ethinyl estradiol tablets) [30]	Combipatch® (estradiol/ norethindrone acetate transdermal system) [31]	Climara Pro® (estradiol/ levonorgestrel transdermal system) [32]	Brisdelle™ (paroxetine) [33]
Manufacturer	Pfizer Inc.	Pfizer Inc.	Pfizer Inc.	Novo Nordisk Inc.	Bayer Healthcare Pharmaceuticals, Inc.	Warner Chilcott Company, LLC.	Noven Pharmaceuticals	Bayer Healthcare Pharmaceuticals, Inc.	Noven Therapeutics, LLC.
VMS indication	Treatment of moderate to severe VMS associated with menopause in women with a uterus	Treatment of moderate to severe VMS due to menopause in women who have a uterus	Treatment of moderate to severe VMS due to menopause in women who have a uterus	Treatment of moderate to severe VMS associated with menopause in women who have a uterus	Treatment of VMS due to menopause in women with an intact uterus	Treatment of moderate to severe VMS due to menopause in women with an intact uterus	Treatment of moderate to severe VMS associated with menopause in women with an intact uterus	Treatment of moderate to severe VMS associated with menopause in women with an intact uterus	Treatment of moderate to severe VMS associated with menopause
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral	Transdermal	Transdermal	Oral
Available doses	CE 0.45 mg/BZA 20 mg	0.3 mg CE/1.5 mg MPA 0.45 mg CE/1.5 mg MPA 0.625 mg CE/2.5 mg MPA 0.625 mg CE/5 mg MPA	0.625 mg CE/5.0 mg MPA (0.625 mg CE alone for days 1-14; 0.625 mg CE/5.0 mg MPA for days 15-28)	1.0 mg estradiol/0.5 mg NETA 0.5 mg estradiol/0.1 mg NETA	0.25 mg DRSP/0.5 mg estradiol 0.5 mg DRSP/1 mg estradiol	0.5 mg NETA/2.5 µg ethinyl estradiol 1 mg NETA/5 µg ethinyl estradiol	0.05 mg estradiol/0.14 mg NETA (9 sq cm) 0.05 mg estradiol/0.25 mg NETA (16 sq cm)	0.045 mg estradiol/0.015 mg levonorgestrel	7.5 mg

		Estrogen-progesterone therapy formulations						SSRI	
	DUAVEE™ (CE/BZA) [1]	Prempro® (CE/ MPA tablets) [27]	Premphase® (CE/ MPA tablets) [27]	Activella® (estradiol/norethindrone acetate tablets) [28]	Angeliq® (drospirenone/ estradiol tablets) [29]	femhrt® (norethindrone acetate/ethinyl estradiol tablets) [30]	Combipatch® (estradiol/ norethindrone acetate transdermal system) [31]	Climara Pro® (estradiol/ levonorgestrel transdermal system) [32]	Brisdelle™ (paroxetine) [33]
Contraindications	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Active deep venous thrombosis, pulmonary embolism, or history of these conditions Active arterial thromboembolic disease (eg, stroke, myocardial infarction) or history of these conditions Hypersensitivity (eg, anaphylaxis, angioedema) to estrogens, BZA, or any ingredients Undiagnosed abnormal uterine bleeding Known, suspected, or past history of breast cancer Known or suspected estrogen-dependent neoplasia Known hepatic impairment or disease Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Pregnancy, women who may become pregnant, and nursing mothers 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Prempro Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Premphase Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Activella Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or history of arterial thromboembolic disease (eg, stroke, myocardial infarction) Renal impairment Liver dysfunction or disease Adrenal insufficiency Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorder Known hypersensitivity to any of the ingredients in Angeliq Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in femhrt Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Combipatch Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Climara Pro Known or suspected pregnancy 	<p>Concurrent use with monoamine oxidase inhibitors or within 14 days of monoamine oxidase inhibitor use</p> <p>Use with thioridazine</p> <p>Use with pimozide</p> <p>Patients with hypersensitivity to any of the ingredients in Brisdelle</p> <p>Pregnancy</p>

	Estrogen-progesterone therapy formulations								SSRI
	DUAVEE™ (CE/BZA) [1]	Prempro® (CE/ MPA tablets) [27]	Premphase® (CE/ MPA tablets) [27]	Activella® (estradiol/norethindrone acetate tablets) [28]	Angeliq® (drospirenone/ estradiol tablets) [29]	femhrt® (norethindrone acetate/ethinyl estradiol tablets) [30]	Combipatch® (estradiol/ norethindrone acetate transdermal system) [31]	Climara Pro® (estradiol/ levonorgestrel transdermal system) [32]	Brisdelle™ (paroxetine) [33]
Warnings and precautions	Duavee™ should not be taken with additional estrogens. Unopposed estrogens have been associated with an increased risk of endometrial cancer, DVT, and probable dementia Breast cancer Ovarian cancer Gallbladder disease Retinal vascular thrombosis Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Hypocalcemia in patients with hypoparathyroidism Exacerbation of symptoms of angioedema in patients with hereditary angioedema Exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangioma Safety has not been established in premenopausal women	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Hyponatremia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of suicidal thinking and behavior Serotonin syndrome Reduced efficacy of tamoxifen Abnormal bleeding Hyponatremia Bone fracture Activation of mania/hypomania Seizures Akathisia Acute angle closure glaucoma Cognitive and motor impairment

CE, conjugated estrogens; BZA, bazedoxifene; VMS, vasomotor symptoms; SSRI, selective serotonin reuptake inhibitor; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; DRSP, drospirenone, VTE, venous thromboembolism.

Osteoporosis

Pharmacologic options approved in the United States for the prevention and treatment of osteoporosis include HT, the SERM raloxifene, bisphosphonates (eg, alendronate, risedronate, ibandronate, zoledronic acid), calcitonin, teriparatide, and denosumab. **Table 2.3** summarizes the product characteristics for the therapeutics that are approved for the prevention and/or treatment of osteoporosis, which may be considered comparators of CE/BZA. As mentioned for VMS, these comparisons are not based on head-to-head comparative trials, but rather provide comparisons based on each product's prescribing information.

Table 2.3. Comparison of CE/BZA With Key Agents Indicated for the Prevention and/or Treatment of Osteoporosis

		Estrogen-progesterone therapy				Bisphosphonates				SERM
	DUAVEE™ (CE/BZA)	Prempro (CE/ MPA tablets) [27]	Premphase (CE/ MPA tablets) [27]	Activella (estradiol/ norethindrone acetate tablets) [28]	femhrt (norethindrone acetate/ethinyl estradiol tablets) [30]	Fosamax® (alendronate sodium tablets or oral solution*) [34]	Boniva® (ibandronate sodium tablets) [35]	Actonel® (risedronate sodium tablets†) [36]	Reclast® (zoledronic acid injection) [37]	Evista® (raloxifene hydrochloride tablet) [38]
Manufacturer	Pfizer Inc.	Pfizer Inc.	Pfizer Inc.	Novo Nordisk Inc.	Warner Chilcott Company, LLC.	Merck & Co., Inc.	Roche Laboratories	Warner Chilcott Company, LLC.	Novartis Pharmaceutica ls	Eli Lilly and Company
Postmenopausal osteoporosis indication	Prevention of postmenopausal osteoporosis in women with a uterus	Prevention of postmenopausal osteoporosis	Prevention of postmenopausal osteoporosis	Prevention of postmenopausal osteoporosis	Prevention of postmenopausal osteoporosis	Treatment and prevention of postmenopausal osteoporosis	Treatment and prevention of postmenopausal osteoporosis	Treatment and prevention of postmenopausal osteoporosis	Treatment and prevention of postmenopausal osteoporosis	Treatment and prevention of postmenopausal osteoporosis
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Injection	Oral
Available doses	CE 0.45 mg/BZA 20 mg	0.3 mg CE/1.5 mg MPA 0.45 mg CE/1.5 mg MPA 0.625 mg CE/2.5 mg MPA 0.625 mg CE/5 mg MPA	0.625 mg CE/5.0 mg MPA (0.625 mg CE alone for days 1-14; 0.625 mg CE/5.0 mg MPA for days 15-28)	1.0 mg estradiol/0.5 mg NETA 0.5 mg estradiol/0.1 mg NETA	0.5 mg NETA/2.5 µg ethinyl estradiol 1 mg NETA/5 µg ethinyl estradiol	10 mg (daily) 70 mg (weekly)	150 mg (monthly)	5 mg (daily) 35 mg (weekly) 75 mg (2 consecutive days per month) 150 mg (once monthly)	5 mg in a 100-mL ready-to-infuse solution (once every 1-2 years)	60 mg

		Estrogen-progesterone therapy				Bisphosphonates				SERM
	DUAVEE™ (CE/BZA)	Prempro (CE/ MPA tablets) [27]	Premphase (CE/ MPA tablets) [27]	Activella (estradiol/ norethindrone acetate tablets) [28]	femhrt (norethindrone acetate/ethinyl estradiol tablets) [30]	Fosamax® (alendronate sodium tablets or oral solution [†]) [34]	Boniva® (ibandronate sodium tablets) [35]	Actonel® (risedronate sodium tablets [†]) [36]	Reclast® (zoledronic acid injection) [37]	Evista® (raloxifene hydrochloride tablet) [38]
Contraindications	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Active deep venous thrombosis, pulmonary embolism, or history of these conditions Active arterial thromboembolic disease (eg, stroke, myocardial infarction) or history of these conditions Hypersensitivity (eg, anaphylaxis, angioedema) to estrogens, BZA, or any ingredients Undiagnosed abnormal uterine bleeding Known, suspected, or past history of breast cancer Known or suspected estrogen-dependent neoplasia Known hepatic impairment or disease Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Pregnancy, women who may become pregnant, and nursing mothers 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Prempro Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Premphase Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in Activella Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active or history of deep vein thrombosis, pulmonary embolism Active or recent arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease Known hypersensitivity to any of the ingredients in femhrt Known or suspected pregnancy 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Abnormalities of the esophagus which delay esophageal emptying (eg, stricture, achalasia) Inability to stand or sit upright for ≥30 minutes Hypocalcemia Hypersensitivity to any of the ingredients in Fosamax Do not administer Fosamax oral solution to patients at increased risk of aspiration 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Abnormalities of the esophagus which delay esophageal emptying (eg, stricture, achalasia) Inability to stand or sit upright for ≥60 minutes Hypocalcemia Hypersensitivity to Boniva 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Abnormalities of the esophagus which delay esophageal emptying (eg, stricture, achalasia) Inability to stand or sit upright for ≥30 minutes Hypocalcemia Hypersensitivity to any of the ingredients in Actonel 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Hypocalcemia Creatinine clearance <35 mL/min Renal impairment Hypersensitivity to any of the ingredients in Reclast 	<p>Patients with any of the following:</p> <ul style="list-style-type: none"> Active or past history of VTE, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis Pregnancy, women who may become pregnant, and nursing mothers

	DUAVEE™ (CE/BZA)	Estrogen-progesterone therapy				Bisphosphonates				SERM
		Prempro (CE/ MPA tablets) [27]	Premphase (CE/ MPA tablets) [27]	Activella (estradiol/ norethindrone acetate tablets) [28]	femhrt (norethindrone acetate/ethinyl estradiol tablets) [30]	Fosamax® (alendronate sodium tablets or oral solution [†]) [34]	Boniva® (ibandronate sodium tablets) [35]	Actonel® (risedronate sodium tablets [†]) [36]	Reclast® (zoledronic acid injection) [37]	Evista® (raloxifene hydrochloride tablet) [38]
Warnings and precautions	Duavee™ should not be taken with additional estrogens. Unopposed estrogens have been associated with an increased risk of endometrial cancer, DVT, and probable dementia Breast cancer Ovarian cancer Gallbladder disease Retinal vascular thrombosis Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Hypocalcemia in patients with hypoparathyroidism Exacerbation of symptoms of angioedema in patients with hereditary angioedema Exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangioma Safety has not been established in premenopausal women	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	Increased risk of myocardial infarction, stroke, pulmonary emboli, deep vein thrombosis, invasive breast cancer, and dementia Endometrial cancer Gallbladder disease Hypercalcemia Visual abnormalities Elevated blood pressure Elevations of plasma triglycerides in patients with preexisting hypertriglyceridemia Poor estrogen metabolism in patients with impaired liver function Recurrence of cholestatic jaundice in patients with a past history Increase in thyroid-binding globulin levels in patients with hypothyroidism Fluid retention Estrogens should be used with caution in patients with severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas	(No boxed warnings) Severe irritation of the upper gastrointestinal mucosa Hypocalcemia Severe bone, joint, and muscle pain Osteonecrosis of the jaw Atypical femur fractures Not recommended for patients with renal impairment	(No boxed warnings) Severe irritation of the upper gastrointestinal mucosa Hypocalcemia Severe bone, joint, and muscle pain Osteonecrosis of the jaw Atypical femoral fractures Not recommended for patients with severe renal impairment	(No boxed warnings) Severe irritation of the upper gastrointestinal mucosa Hypocalcemia Severe bone, joint, and muscle pain Osteonecrosis of the jaw Atypical femur fractures Not recommended for patients with severe renal impairment	(No boxed warnings) Hypocalcemia Renal toxicity Osteonecrosis of the jaw Atypical femur fractures Risk during pregnancy Severe bone, joint, and muscle pain	Increased risk of deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, and fatal stroke Cardiovascular disease Not recommended in premenopausal women Use with caution in patients with hepatic impairment Hypertriglyceridemia Not recommended for concomitant use with systemic estrogens Use with caution in patients with moderate or severe renal impairment Unexplained uterine bleeding or breast abnormalities

CE, conjugated estrogens; BZA, bazedoxifene; SERM, selective estrogen receptor modulator; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; VTE, venous thromboembolism.

^{*}Other brand names available include Fosamax Plus D® and Binosto®.

[†]Other brand name available is Atelvia®.

2.2 Place of Product in Therapy

2.2.1 Disease Description

According to the World Health Organization (WHO) and the Stages of Reproductive Aging Workshop (STRAW) working group, menopause may be defined as “the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation” [39]. Natural menopause is associated with aging and typically occurs from age 40 to 58 years, on average at age 51 [40]. The loss of ovarian function and transition to menopause varies from individual to individual [41]. Nevertheless, a general pattern for reproductive aging has been recognized and serves as the basis for the staging system that was outlined by the STRAW working group in 2001 [42] and updated in 2011 [43]. This staging system includes 3 major phases: the reproductive phase, menopausal transition, and postmenopause (**Figure 2.1**) [43,44]. The menopausal transition is divided into 2 stages: an early stage, characterized by variable cycle length and elevated follicle stimulating hormone (FSH) levels; and a late stage, characterized by an amenorrhea interval of at least 60 days and elevated FSH levels (>25 IU/L) [43]. The final menstrual period (FMP) marks the end of the menopausal transition and the start of postmenopause [43]. During early postmenopause, FSH levels continue to increase and estradiol levels decrease; at approximately 2 years following the FMP, both begin to level off [43]. Early postmenopause encompasses the 12-month period of amenorrhea that is used to define the FMP and menopause [43]. Together, this 12-month period and the menopausal transition are commonly known as perimenopause [43]; a woman is considered to have gone through menopause at the end of this 12 month-period of amenorrhea if there is no obvious pathologic or physiologic cause for the cessation of menstruation [39].

During the late reproductive phase and menopausal transition, ovarian function declines, leading to large fluctuations in estrogen levels [45]. The fluctuating levels of estrogens during perimenopause may lead to physical symptoms such as hot flashes, night sweats, headaches, dizziness, rapid or irregular heartbeat, atrophic vaginitis, bladder irritability, mood changes, sleep disturbances, aches and pains, and malaise [46,47]. VMS, including hot flashes and night sweats, are most common during the late stage of the menopausal transition and early postmenopause [43]. In addition to these symptoms, the menopausal transition is also associated with reductions in bone mass and an increased risk for osteoporosis [48].

Figure 2.1. The STRAW +10 staging system for reproductive aging in women. Reprinted with permission from Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause*. 2012;19(4):387-95.

Stage	Menarche			FMP (0)						
	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	Reproductive				Menopausal transition		Postmenopause			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				Variable	1-3 years	2 years (1+1)		3-6 years	Remaining lifespan
Principal criteria										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/length	Variable length Persistent ≥7 day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
Supportive criteria										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L† Low Low	↑ Variable Low Low	Stabilizes Very low Very low		
Antral follicle count			Low	Low	Low	Low	Very low	Very low		
Descriptive characteristics										
Symptoms						Vasomotor symptoms <i>Likely</i>	Vasomotor symptoms <i>Most likely</i>			Increasing symptoms of urogenital atrophy

STRAW, Stages of Reproductive Aging Workshop; FMP, final menstrual period; FSH, follicle stimulating hormone; AMH, antimüllerian hormone.

*Blood draw on cycle days 2-5.

† Approximate expected level based on assays using current international pituitary standard.

Epidemiology and Relevant Risk Factors

Vasomotor Symptoms

Globally, the number of postmenopausal women is expected to reach 1.1 billion by 2025 [40], and a high percentage of these women will likely experience menopausal symptoms, including VMS [49]. An estimated 35% to 50% of women will experience VMS during perimenopause and 30% to 80% of women will experience VMS during postmenopause [49]. The prevalence of VMS varies by country, region, and ethnic group [46], and estimates of the number of women experiencing VMS depend on symptom reporting and may be influenced by culture, race, and geographic factors [46]. For example, in a study of 16,065 women 40 to 55 years of age in the United States, the prevalence of VMS was approximately 18% among Japanese women, 21% among Chinese women, 31% among Caucasian women, 35% among Hispanic women, and 46% among African American women [50].

Risk factors associated with the development of VMS include a number of demographic, socioeconomic, and lifestyle-related factors [51,52]. Women who are in the late stage of the menopausal transition or early postmenopause are most likely to experience VMS [44,52]. High body mass index (BMI) and African American race are also positively associated with the development of VMS [51,52]. Current smokers and women with higher levels of anxiety or depression are also more likely to experience VMS, as are women with less than a college education or the inability to pay for their basic needs [51,52]. In addition, some breast cancer treatments may be associated with the development of VMS [53].

Osteoporosis

Osteoporosis affects more than 8 million women over the age of 50 in the United States [54] and more than 12 million women aged 50 to 84 across France, the United Kingdom, Germany, Italy, and Spain [55]. The prevalence of osteoporosis in women generally increases with age [55]. Although differences have been observed in the prevalence of osteoporosis between ethnic groups, it is difficult to directly compare rates between countries due to differences in the populations analyzed [56]. Osteoporotic fractures are a common complication associated with osteoporosis; the lifetime risk of sustaining an osteoporotic fracture is approximately 50% for women 50 years of age [57].

In addition to advanced age and female gender, there are a number of clinical factors associated with an increased risk of osteoporotic fracture [54,55]. These include the following:

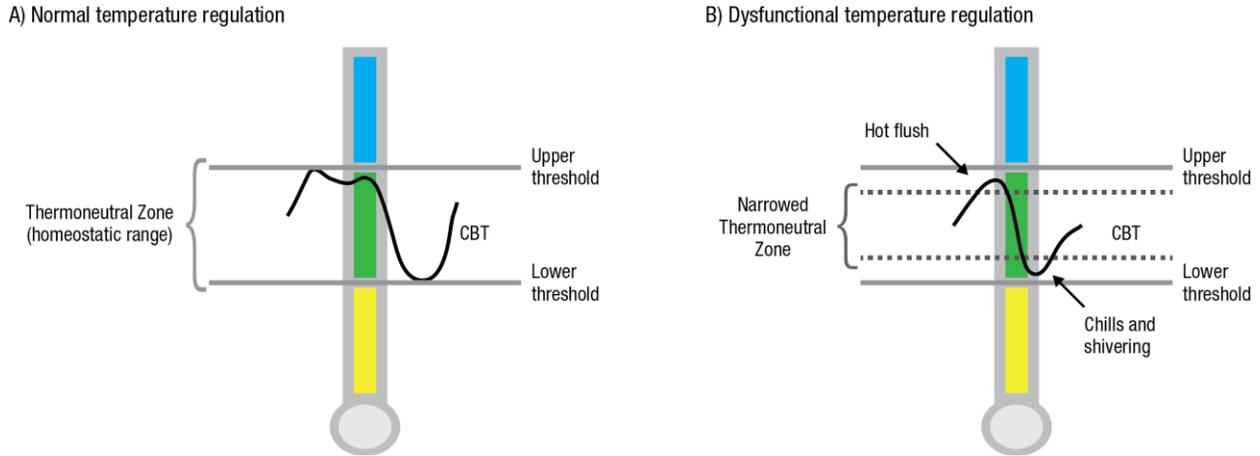
- Low BMI
- Personal or family history of fragility fractures
- Asian or Caucasian ethnicity
- Current smoking
- High alcohol intake (>3 beverages/day)
- Rheumatoid arthritis
- Hypogonadism
- Inflammatory bowel disease
- Extended periods of inactivity
- Organ transplantation
- Endocrine disorders
- Chronic obstructive pulmonary disease

Pathophysiology

Vasomotor Symptoms

Changes in estrogen levels during the menopausal transition may affect the thermoregulatory pathway, leading to occurrence of VMS [45,51]. While the specific pathophysiology underlying menopause-related VMS is not understood, there are several proposed mechanisms [45,51]. The foremost hypothesis is that the transition to menopause affects the optimal temperature range (known as the thermoneutral zone) for the core body temperature (CBT; **Figure 2A**) [45,51]. An increase in the CBT above the thermoneutral zone induces peripheral vasodilation and sweating and a decrease in the CBT below this range induces peripheral vasoconstriction and shivering [45,51]. In menopausal women experiencing VMS, the thermoneutral zone is thought to be narrowed, resulting in an excessive response to a relatively minor increase in CBT (**Figure 2B**) [45,51]. An alternative hypothesis to the narrowing of the thermoneutral zone is that VMS result from a decrease in the reactivity of the peripheral vasculature (which is affected by both estrogen and progesterone levels) to changes in body temperature, ultimately resulting in a delayed and exaggerated vasodilatory response [45,51]. Another proposed mechanism of action involves the effects of estrogen on neurochemical levels, such as serotonin and norepinephrine [45,47,51]. Both of these neurotransmitters contribute to regulation of temperature homeostasis and are affected by fluctuating hormone levels associated with menopause [47,58-60]. In addition, dysregulation of serotonin and norepinephrine have been associated with hot flushes and night sweats [58,61].

Figure 2.2. Thermoneutral zone in (A) normal core body temperature regulation, and (B) dysfunctional temperature regulation associated with VMS. Reprinted with permission from Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. *Arch Womens Ment Health.* 2007;10(6):247-57.



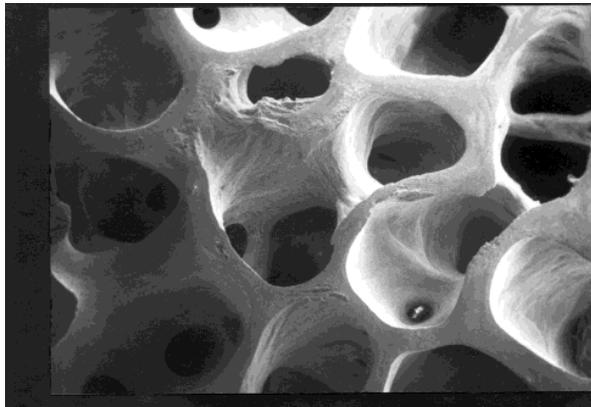
VMS, vasomotor symptoms; CBT, core body temperature.

Osteoporosis

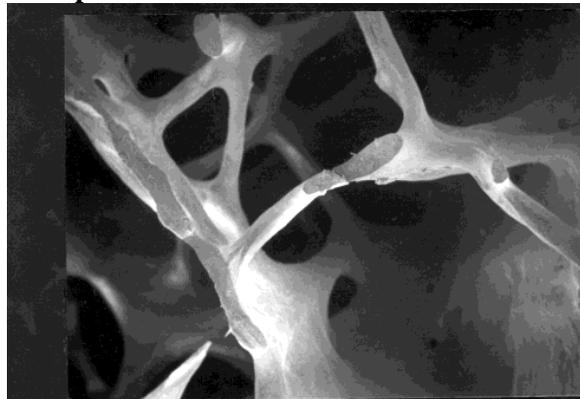
Alterations in the bone remodeling process that occur with increasing age and the onset of menopause lead to decreased bone mass and weakening of the skeletal architecture, resulting in the increased bone fragility and fracture risk that characterize osteoporosis [22,62]. Bone remodeling involves a balance of the processes of bone formation and bone resorption [22,62]. The decline in estrogen levels associated with menopause results in a reduction in estrogen-mediated inhibition of bone resorption, and shifts the balance towards bone resorption without an adequate increase in the rate of bone formation [22]. The onset of menopause is also accompanied by an increase in the bone remodeling rate, which exacerbates the negative effects of this imbalance on the bone architecture [62]. Elevated levels of bone turnover markers in the serum or urine are indicative of bone remodeling and bone loss in women with osteoporosis [22,62]. Bone turnover markers may be indicative of bone resorption (eg, N-telopeptides, C-telopeptides) or bone formation (eg, bone-specific alkaline phosphatase, osteocalcin) [22]. The consequences of the shift in the bone remodeling process are a significantly weakened bone structure and reduced bone mass (**Figure 2.3**) [62].

Figure 2.3. Normal and osteoporotic bone. Reprinted with permission from *Clinician's Guide to Prevention and Treatment of Osteoporosis*, 2013. National Osteoporosis Foundation, Washington, DC 20037.

Normal bone



Osteoporotic bone



Clinical Presentation

Vasomotor Symptoms

VMS include hot flushes and accompanying night sweats [51]. Hot flushes, which typically last from 1 to 5 minutes, are characterized by a sudden feeling of warmth, often accompanied by a rapid heart rate, flushing, and excessive sweating [51]. A woman may experience multiple hot flushes over the course of the day and night; night-time episodes are often associated with night sweats [51]. The prevalence and severity of VMS have been shown to be related to the stage of menopause [52,63]. VMS are likely to occur late in the menopausal transition and typically continue into postmenopause, but tend to decrease in prevalence and severity over time [43,63]. A meta-analysis examining the duration of VMS found that the prevalence peaked at 1 year after FMP [64]. Although the median duration of symptoms in that meta-analysis was approximately 4 years, approximately 10% of women reported symptoms up to 12 years after the FMP [64]. In a separate population-based cohort study, the median duration of moderate or severe hot flushes was 10.2 years, and the duration was longer for women with an earlier onset of VMS than for those with an initial onset of moderate or severe hot flushes in the late menopausal transition or postmenopause [65].

Osteoporosis

Osteoporosis is an asymptomatic skeletal disease leading to decreased bone mass and an increased risk of fractures [48]. Postmenopausal women with osteoporosis may experience a 3% to 5% annual bone loss, resulting in a loss of up to 40% of their peak bone mass over the course of a lifetime; by comparison, the normal annual rate of age-associated bone loss is only 1% [48]. Clinical manifestations of osteoporosis may include osteoporotic fractures, most commonly at the hip, spine, and wrist, and associated complications [48]. Hip and spine fractures are associated with a particularly poor prognosis and often result in long-term disability, and is associated with increased mortality [48].

Societal, Humanistic and/or Economic Burden of VMS and Osteoporosis

Vasomotor Symptoms

Humanistic Burden

VMS have been shown to substantially impact QOL and may be associated with anxiety, sleep problems, mood disturbances, fatigue, decreased cognitive function, and depression [66-69]. Study results have shown a statistically significant relationship between moderate to severe hot flashes and decreased QOL as measured by the Short Form-36 (SF-36) Health Survey [66]. A recent cohort study reported significantly lower mean health status scores in women with moderate and severe VMS compared with women with no symptoms [70]. VMS can have a substantial impact on physical and psychosocial well-being. The reduced QOL associated with these issues may contribute to anxiety and social isolation, leading to work, personal, and social disruptions [66].

Economic Burden

There are very few studies on the economic burden of menopausal symptoms. The direct, health care-related costs for VMS may include the initial general practitioner or gynecologist visit, follow-up visits once medication has been prescribed, prescription and over-the-counter medication costs, counseling for mood disturbances, and neurologist visits for sleep problems, cognitive issues, or headaches [66]. Indirect costs may include lost productivity and increased personal costs [66,71].

A recent study evaluated the economic burden of VMS in postmenopausal women and showed that presence of VMS had a significant impact on health status, work productivity, and health care resource use, particularly in women with more severe symptoms [70]. For example, women with severe and moderate VMS had significantly lower mean health status scores compared with women with no symptoms ($P < 0.0001$), and mean number of menopause symptom-related physician visits was significantly greater for women with severe, moderate, or mild symptoms than for women without symptoms ($P < 0.0001$). In another recent study, higher medical ($P < 0.0001$), pharmacy ($P < 0.0001$), and sick leave costs ($P < 0.0001$) were observed among employees with diagnosed menopausal symptoms compared with those without [71]; significantly lower productivity (hourly and yearly; $P = 0.0072$ and $P = 0.0135$, respectively) was also observed in subjects with diagnosed menopausal symptoms.

Osteoporosis

Humanistic Burden

Osteoporotic fractures may be associated with a significant negative impact on QOL [72,73]. In a study of 86,128 postmenopausal women (2,257 of whom reported a new osteoporotic fracture during the 2-year study period), SF-12 Physical Component Summary Scores, which served as a measure of health-related QOL, were significantly lower for women of all ages who had suffered hip, spine, or rib fractures than for those without fractures ($P \leq 0.004$) [72]. In a separate study of 57,141 postmenopausal women, scores on health-related QOL assessments (including European Quality of Life-5 Dimensions Index health-utility scores, and SF-36 health status, physical function, and vitality scores) decreased with increasing numbers of prior fracture locations [73]. In addition, osteoporosis-related fractures are associated with serious physical and psychological consequences such as functional impairment and disability, depression, pain, and increased mortality [54]. Osteoporotic hip fractures are associated with particularly poor patient outcomes such as a higher risk of future fractures and up to a 20% increase in the risk of mortality within the year following the fracture [54].

Economic Burden

The economic burden of osteoporosis is substantial and includes direct costs (eg, outpatient visits, osteoporosis medications, hospitalizations, and nursing home care) and indirect costs related to the morbidity associated with osteoporotic fractures [74]. In a study of the health care costs for women who were 45 years of age and older, the estimated annual cost for treating osteoporosis (including costs related to hospital inpatient and outpatient services, physician office visits, nursing home care, emergency department visits, and home and hospice care) was \$12.9 billion USD in 1997 [75]. Based on a separate analysis of Medicare costs related to osteoporotic fractures in women 65 years of age and older, treatment costs for the estimated 2.39 million fractures occurring during the 3-year period from 2001 to 2003 were approximately \$12.96 billion USD; costs related to hospitalization and long-term care accounted for more than 90% of total Medicare costs [76].

2.2.2 Approaches to Treatment for Menopausal Symptoms and Prevention of Osteoporosis

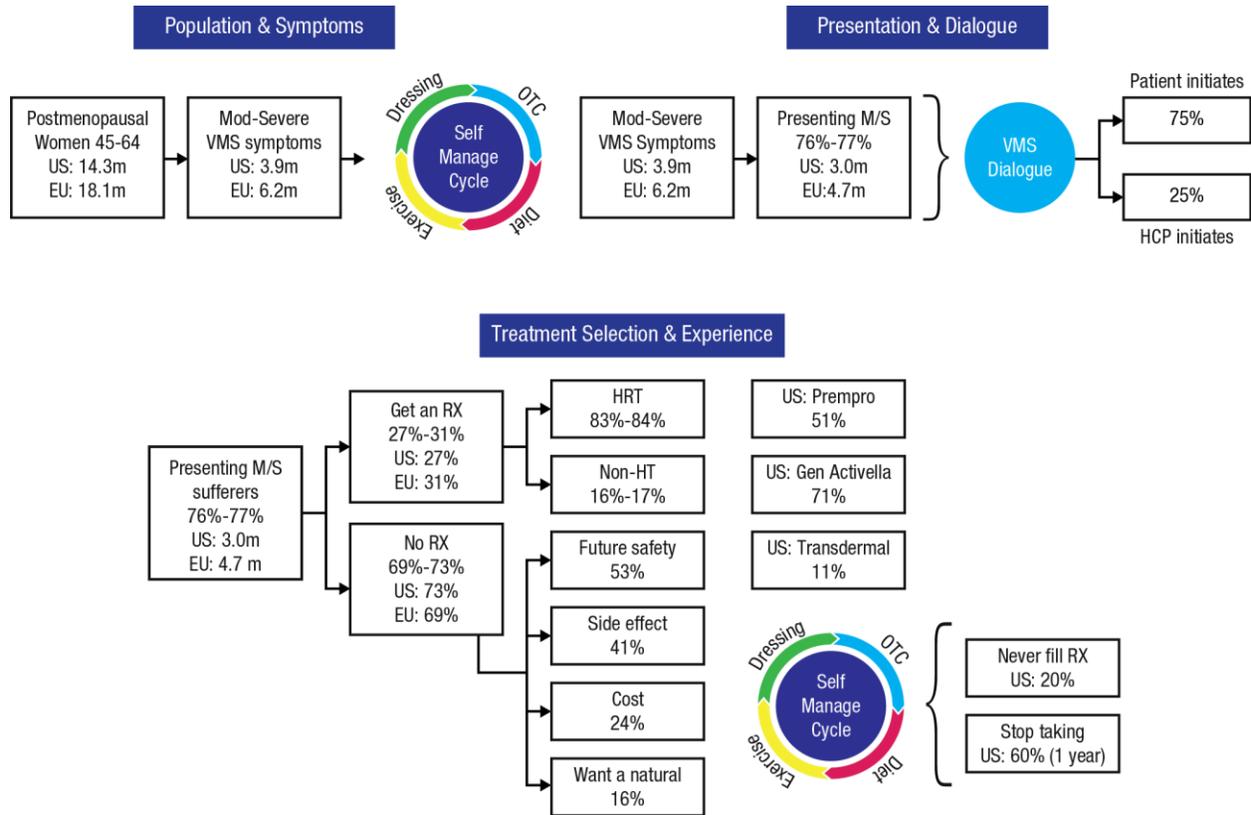
Principal Options/Practice Patterns

Vasomotor Symptoms

HT, either as estrogen therapy (ET) alone or EPT, is the current standard of care for the treatment of VMS [19]. ET alone has been associated with an elevated risk of endometrial cancer in women with an intact uterus [19] and should only be considered for women who have had a hysterectomy [19]. EPT is recommended for nonhysterectomized women because the progestogen component of EPT counters the stimulatory effects of systemic estrogens on the uterus [19]. A typical patient journey for nonhysterectomized women with VMS is illustrated in **Figure 2.4**.

HT is considered to be the most effective treatment option for the relief of VMS [19,77]. When prescribed for the appropriate women, the benefit-risk profile of HT is generally favorable over relatively long treatment periods of up to 3 to 5 years for EPT and a median of 7 years for ET [19]. Nevertheless, professional organizations suggest that HT administration should be highly individualized with clear discussions with HT candidates of the risks and benefits associated with treatment [19,20]. The primary safety concerns that may be associated with HT include an increased risk of breast cancer (particularly EPT), stroke, and VTE [19]. Potential side effects of estrogen-based therapy include breast tenderness, irregular vaginal bleeding, nausea and vomiting, headache, dizziness, weight gain, and rash [77], as well as new-onset or worsening stress urinary incontinence (EPT only) [19]. Tolerability concerns associated with the use of progestins in postmenopausal women may include breakthrough vaginal bleeding, breast pain, increased breast density, mood swings, bloating, fluid retention, and sleep disturbance [19,21,78].

Figure 2.4. Typical patient journey for nonhysterectomized women with VMS. [87]



VMS, vasomotor symptoms; OTC, over-the-counter; HCP, health care provider; HRT, hormone replacement therapy; HT, hormone therapy.

Osteoporosis

Osteoporosis management involves both prevention and treatment strategies; the information presented here focuses on preventative measures. Lifestyle changes, such as increasing calcium and vitamin D intake or performing weight-bearing exercises, can be effective in preventing osteoporosis [22,62]. Supplementation with vitamin D in combination with calcium has been shown to reduce the rate of postmenopausal bone loss and has been associated with a reduction in the risk of osteoporotic fractures [22]. Regular weight-bearing exercise has likewise been associated with an increase in BMD and may also improve balance and agility, which may reduce the risk of falls and resulting osteoporotic fractures [22,62].

For postmenopausal women at low risk of developing osteoporosis, these types of lifestyle changes may be sufficient preventative measures [22]. Pharmacologic treatment should be considered for women aged ≥ 50 years with any of the following risk factors: a hip or vertebral fracture; femoral neck, total hip, or lumbar spine T-score ≤ -2.5 ; or low BMD (femoral neck or spine T-score between -1.0 and -2.5) and 10-year probability of hip fracture $\geq 3\%$ or of a major osteoporotic fracture $\geq 20\%$ based on the WHO's Fracture Risk Analysis (FRAX[®]) algorithm [22,62]. FRAX is a computer-based algorithm that uses a selected list of risk variables to calculate the 10-year probability of hip fracture and major osteoporotic fracture (eg, wrist, humerus, hip, or clinical vertebral fracture) [79].

The major pharmacologic options for the prevention of osteoporosis are bisphosphonates, raloxifene, and HT [22]. Bisphosphonates are recommended as first-line therapy for the prevention of osteoporosis [22]. Bisphosphonate therapy has been associated with significant increases in spine and hip BMD and an up to 70% reduction in the risk of vertebral fractures [22]. The most common tolerability problem associated with bisphosphonates is irritation of the esophagus and upper gastrointestinal tract [22]. Like bisphosphonate therapy, raloxifene has been associated with improvements in BMD and reductions in the risk of vertebral fracture [22]. Key safety concerns associated with raloxifene include an increased risk of thromboembolism and fatal stroke [38]. Systemic HT has been shown to increase BMD and decrease the risk of vertebral fracture in postmenopausal women [22]. As described previously, HT may be associated with tolerability or safety concerns, and the benefits and risks of initiating HT must be carefully weighed [22]. Individualized pharmacologic treatment is critical for optimizing osteoporosis management [23].

Alternative Treatment Options (Both Drug and Non-Drug)

Menopausal Symptoms

Prescription nonhormonal therapies may be prescribed off-label for women with VMS who cannot or choose not to take HT, but these treatments may be associated with poor efficacy relative to HT as well as safety and tolerability concerns [80]. Options include selective serotonin reuptake inhibitors (SSRIs; eg, paroxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine), antihypertensives (eg, clonidine and methyl dopa), and anticonvulsants (eg, gabapentin) [77,81]. Nonprescription herbal and biologically based therapies, including black cohosh and phytoestrogens (eg, soy protein, red clover isoflavones), are also commonly used to treat VMS [77,81]. Although there is some evidence for the efficacy of SSRIs, SNRIs, clonidine, and gabapentin for the management of VMS, these treatments are generally less effective than HT [77,80]. Data for the efficacy of soy isoflavone and other herbal and biologically based therapies are limited and often conflicting [77,80]. Other nonpharmacologic strategies for managing VMS include lifestyle modifications (eg, stress reduction), use of breathing and relaxation techniques, and increased physical activity [81].

Osteoporosis

As described briefly in section 2.2.2.1.2, there are a number of nonpharmacological strategies recommended for managing osteoporosis. These include lifestyle modifications (eg, improved nutrition, exercise, smoking cessation, alcohol moderation), fall prevention strategies, and calcium and vitamin D supplementation [22,62]. These strategies are recommended for the general population and may be sufficient for preventing osteoporosis in low-risk women [22,62]. In addition, there are several medications that may be prescribed off-label for the prevention or treatment of osteoporosis, including the synthetic vitamin D analogue calcitriol and other bisphosphonates (eg, etidronate, pamidronate, tiludronate) [62]. An isoflavone phytoestrogen product, genistein, may also be used for the prevention or treatment of osteoporosis [62]. In general, data demonstrating efficacy for osteoporosis (ie, reduction in fracture risk) is lacking for these off-label prescription and nonprescription treatments [62].

Place and Anticipated Use of CE/BZA in the Treatment of Moderate to Severe VMS and Prevention of Osteoporosis

In women with a uterus seeking treatment for moderate to severe VMS or who would also benefit from protection from bone loss, there is an underserved medical need for therapies that provide endometrial protection with improved tolerability compared with EPT [19,24]. Although adding a progestogen to CE provides endometrial protection, the combination is associated with safety and tolerability concerns that may affect treatment adherence [82]. CE/BZA represents a novel approach to effectively treat menopausal symptoms and prevent bone loss while protecting the endometrium [24]. CE/BZA may be an

alternative to traditional HT for the treatment of VMS in nonhysterectomized, postmenopausal women [24]. CE/BZA may also provide a favorable new option to HT for the prevention of postmenopausal osteoporosis [25].

Proposed Ancillary Disease or Care Management Intervention Strategies

None to report.

Expected Outcomes of Therapy

Based on results of the SMART phase 3 pivotal trials in postmenopausal women with an intact uterus, CE/BZA was associated with significant reductions in the number and severity of hot flashes at Week 12 compared with placebo, significant improvements in lumbar spine and total hip BMD from baseline versus placebo, and significant decreases in bone turnover markers from baseline compared with placebo over 2 years [5,6,11]. Results of the SMART studies also indicated that CE/BZA had beneficial effects on sleep and QOL, based on the Menopause-specific Quality of Life (MENQOL) questionnaire, and was associated with greater satisfaction with treatment, based on the Menopause Symptoms-Treatment Satisfaction Questionnaire (MS-TSQ), compared with placebo [9,10,12,15]. Based on adverse event data from studies up to 2 years in duration, no increased risk of VTEs or cardiovascular events was observed with CE/BZA compared with placebo [6]. Rates of endometrial hyperplasia <1% were observed with CE/BZA over 2 years [4]; these rates are consistent with the endometrial safety standard established by the FDA (endometrial hyperplasia rate $\leq 1\%$) [18]. CE/BZA demonstrated noninferiority to placebo for change from baseline at 1 year in mammographic breast density, and the incidence of breast pain/tenderness with CE/BZA was comparable to placebo and significantly lower than that observed with CE/MPA [16]. CE/BZA demonstrated a vaginal bleeding profile similar to placebo and significantly better than that observed with CE/MPA. More complete details on the clinical benefits and safety and tolerability profile of CE/BZA are provided in Section 3 of this dossier.

Other Drug Development or Postmarketing Obligations

None to report.

Other Key Assumptions and Their Rationale

None to report.

2.2.3 Relevant Treatment Guidelines and Consensus Statements from National and/or International Bodies

Several organizations have developed guidelines for the treatment of menopausal symptoms and the prevention/treatment of postmenopausal osteoporosis. The key guidelines for the treatment of menopausal symptoms from the updated 2013 International Menopause Society recommendations on menopausal HT and from the 2012 HT position statement from the North American Menopause Society are summarized in **Table 2.4**. The key guidelines from the 2010 position statement on the management of osteoporosis in postmenopausal women from the North American Menopause Society and from the 2013 International Osteoporosis Foundation *Clinician's Guide to Prevention and Treatment of Osteoporosis* are summarized in **Table 2.5**.

Table 2.4. Key Clinical Guidelines for the Treatment of VMS With HT

<p>Updated 2013 International Menopause Society recommendations on menopausal HT [20]</p> <ul style="list-style-type: none"> • HT is the most effective option for treating moderate to severe menopausal symptoms and the greatest benefits are achieved within 10 years of menopause or in women <60 years of age • In women with premature menopause, HT is recommended until the average age of natural menopause • Duration and doses of HT should be individualized to meet personal treatment goals • Estrogen alone is appropriate in women after hysterectomy; progestogen/progesterone must be added to provide endometrial protection for nonhysterectomized women • HT is not associated with an increased coronary disease risk in healthy women <60 years of age or within 10 years of menopause • HT-associated risk of breast cancer is small and decreases after treatment discontinuation • Insufficient safety data exists to support HT use in breast cancer survivors • HT is associated with an elevated risk of VTE and ischemic stroke, but these events are rare in women <60 years of age • The use of compounded HT is not recommended
<p>North American Menopause Society 2012 HT position statement [19]</p> <ul style="list-style-type: none"> • HT is the most effective option for the treatment of VMS associated with menopause • Individualized risk-benefit assessment is a key component of the decision-making process for initiating HT • The duration of EPT therapy is limited by the increase in breast cancer risk and mortality associated with 3-5 years of use. For ET, the benefit-risk profile has been shown to be more favorable over a mean of 7 years of use • Women with premature or early menopause who are candidates for HT may use HT at least until the median age of natural menopause (51 years) • There is a lack of safety data to support the use of ET in breast cancer survivors • The risk of VTE and stroke is lower with transdermal and low-dose oral estrogen than with standard oral estrogen doses

VMS, vasomotor symptoms; HT, hormone therapy; VTE, venous thromboembolism; EPT, estrogen-progestogen therapy; ET, estrogen therapy.

Table 2.5. Key Clinical Guidelines for the Treatment of Osteoporosis**National Osteoporosis Foundation 2013 *Clinician's Guide to Prevention and Treatment of Osteoporosis** [62]****General principles:**

- Obtain a detailed patient history pertaining to clinical risk factors for osteoporosis-related fractures and falls
- Perform physical examination and obtain diagnostic studies to evaluate for signs of osteoporosis and its secondary causes
- Modify diet/supplements and other clinical risk factors for fracture
- Estimate patient's 10-year probability of hip and any major osteoporosis-related fracture using the US-adapted FRAX algorithm
- Decisions on whom to treat and how to treat should be based on clinical judgment using this guide and all available clinical information

Consider FDA-approved medical therapies based on the following:

- Vertebral fracture (clinical or asymptomatic) or hip fracture
- Hip DXA (femoral neck or total hip) or lumbar spine T-score ≤ -2.5
- Low bone mass (osteopenia) and a US-adapted WHO 10-year probability of a hip fracture $\geq 3\%$ or 10-year probability of any major osteoporosis-related fracture $\geq 20\%$
- Patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Consider nonmedical therapeutic interventions:

- Modify risk factors related to falling
- Consider referrals for physical and/or occupational therapy evaluation (eg, walking aids and other assistive devices)
- Weight bearing, muscle strengthening and balance training

Follow up:

- Patients not requiring medical therapies at the time of initial evaluation should be clinically re-evaluated when medically appropriate
- Patients taking FDA-approved medications should have laboratory and bone density re-evaluation after 2 years, or more frequently when medically appropriate
- Vertebral imaging should be repeated if there is documented height loss, new back pain, postural change, or suspicious finding on chest x-ray following the last (or first) vertebral imaging test
- Regularly, and at least annually, assess compliance and persistence with the therapeutic regimen

North American Menopause Society 2010 position statement on the management of osteoporosis [22]

- All postmenopausal women should adapt lifestyle practices that reduce the risk of fracture and loss of BMD (eg, maintaining a healthy weight, adequate vitamin C and D intake)
- Height and weight should be measured annually and clinical risk factors, presence of back pain, and kyphosis should be assessed
- BMD testing should be considered for postmenopausal women ≥ 50 years of age if they have any of the following risk factors: previous postmenopausal fracture, thinness (body weight < 127 lbs or BMI < 21 kg/m²), parental history of hip fracture, current smoker, rheumatoid arthritis, excessive alcohol consumption
- DXA is the preferred method for BMD testing
- Routine clinical use of bone turnover markers is not recommended
- Vertebral fracture must be confirmed (loss of $> 20\%$ of the anterior, mid, or posterior vertebral dimension) by lateral spine radiographs or VFA visualization during BMD testing
- Adequate calcium intake (1,200 mg/day for adults ≥ 50 years of age) and vitamin D (800-1,000 IU/day) intake is a key component of any osteoporosis prescription drug regimen
- Osteoporosis drug therapy is recommended for all postmenopausal women who meet any of the following criteria:
 - History of osteoporotic vertebral or hip fracture
 - BMD values consistent with osteoporosis (ie, T-scores ≤ -2.5) at the lumbar spine, femoral neck, or total hip
 - T-scores from -1.0 to -2.5 and a 10-year FRAX risk of major osteoporotic fracture (eg, spine, hip, shoulder, and wrist) $\geq 20\%$ or of hip fracture $\geq 3\%$
- Barriers to adherence should be addressed
- During the course of therapy, treatment choice and goals should be periodically re-evaluated. BMD measurement may be repeated after 1-2 years of treatment, although repeated BMD testing is of limited value for a woman on stable therapy
- For untreated postmenopausal women, repeated DXA testing is of limited value until 2-5 years have passed
- Bisphosphonates are the first-line treatments for postmenopausal women with osteoporosis
- Raloxifene is typically considered for postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis
- Teriparatide should typically only be offered to postmenopausal women with osteoporosis who are at high risk of fracture
- HT is primarily indicated for moderate to severe menopause symptoms but may be a treatment option for osteoporosis, including in early postmenopause
- Calcitonin is not a first-line treatment, but may be an option for women > 5 years postmenopause
- Data are lacking regarding the efficacy and safety of combining osteoporosis therapies

- Long-term treatment of osteoporosis is typically required
- Appropriate strategies for managing drug-related adverse effects should be pursued prior to switching to another medication
- Decisions regarding the discontinuation of treatment should be based on individual fracture risk and response to treatment

FRAX, Fracture Risk Analysis; FDA, Food and Drug Administration; DXA, dual-energy X-ray absorptiometry; WHO, World Health Organization; BMD, bone mineral density; VFA, vertebral fracture assessment; BMI, body mass index; HT, hormone therapy.

* Reprinted with permission from *Clinician's Guide to Prevention and Treatment of Osteoporosis*, 2013. National Osteoporosis Foundation, Washington, DC 20037.

† Reprinted with permission from Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause*. 2010;17(1):25-54.

2.3 Evidence for Pharmacogenomic Tests and Drugs

Pfizer is not aware of any relevant pharmacogenomic tests at this time.

3.0 SUPPORTING CLINICAL EVIDENCE

The clinical development program for CE/BZA comprised 26 clinical trials, including 20 phase 1 studies, 1 phase 2 study, and 5 phase 3 studies [83]. The dose selection (CE 0.45 mg/BZA 20 mg) and intended indications for CE/BZA are supported by 4 phase 3 studies (**SMART-1**, **SMART-2**, **SMART-3**, and **SMART-5**); **SMART-4** was considered a supportive trial for regulatory filings. While the **SMART-4 trial** was being conducted, results of CE/BZA bioequivalence testing revealed that the bioavailability of 1 of the BZA formulations used in **SMART-4** was approximately 18% lower than that used in **SMART-1** [3]. Thus, only general safety analyses from the **SMART-4 trial** will be discussed.

This section will present efficacy data from the **SMART-1**, **SMART-2**, **SMART-3**, and **SMART-5** trials for the labeled indications and dosing of CE/BZA, as well as complete data on safety and other outcomes for all the SMART phase 3 studies.

A summary of the CE/BZA phase 3 program, consisting of 5 placebo-controlled, double-blind studies, is shown in **Table 3.1**.

Table 3.1. CE/BZA Phase 3 Summary of Clinical Experience

Study	N	Treatment arms (mg)	Key endpoints
SMART-1 (Study 303) [4-10]	3,397	<ul style="list-style-type: none"> • CE 0.45/BZA 10, 20, 40 • CE 0.625/BZA 10, 20, 40 • Raloxifene 60 (control) • Placebo (control) 	<ul style="list-style-type: none"> • Endometrial hyperplasia at 12 months • BMD at 24 months • VMS at 3 months • Vaginal maturation at 6 months • Breast density at 24 months
SMART-2 (Study 305) [11-13]	318	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • Placebo (control) 	<ul style="list-style-type: none"> • VMS at 3 months
SMART-3 (Study 306) [14,15]	652	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • BZA 20 (control) • Placebo (control) 	<ul style="list-style-type: none"> • VVA at 3 months
SMART-4 (Study 304) [3]	1,061	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • CE 0.45/MPA 1.5 (control) • Placebo (control) 	<ul style="list-style-type: none"> • Endometrial hyperplasia at 12 months • BMD at 12 months
SMART-5 (Study 3307) [16]	1,843	<ul style="list-style-type: none"> • CE 0.45/BZA 20 • CE 0.625/BZA 20 • BZA 20 • CE 0.45/MPA 1.5 (control) • Placebo (control) 	<ul style="list-style-type: none"> • BMD (efficacy) at 12 months • Endometrial hyperplasia (safety) at 12 months • Breast density at 12 months

Secondary endpoints included cumulative amenorrhea (**SMART-1** and **SMART-5**) and breast pain (**SMART-1**, **SMART-2**, and **SMART-5**).

CE, conjugated estrogens; BZA, bazedoxifene; SMART, Selective estrogens, Menopause, And Response to Therapy; BMD, bone mineral density; VMS, vasomotor symptoms; VVA, vulvar/vaginal atrophy; MPA, medroxyprogesterone acetate.

3.1 Summarizing Key Clinical Studies

The summaries below regarding DUAVEE™ (conjugated estrogens/bazedoxifene) include information of an off-label nature. Pfizer does not suggest or recommend the use of DUAVEE™ in any manner other than as described in the Prescribing Information approved by the US Food and Drug Administration (FDA). On October 3, 2013, the FDA approved DUAVEE™ 0.45 mg/20 mg for the treatment of moderate to severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis. At that time, the FDA also issued a Complete Response Letter (CRL) declining approval of conjugated estrogens 0.524 mg/bazedoxifene 20 mg tablets in women with a uterus for the treatment of moderate to severe vulvar/vaginal atrophy (VVA) associated with menopause, for the treatment of moderate to severe vasomotor symptoms associated with menopause, and for the prevention of postmenopausal osteoporosis. The FDA determined that the data submitted were insufficient to grant approval for this indication (VVA) and dose. Pfizer is committed to working with the FDA to determine next steps.

3.1.1 Published and Unpublished Clinical Studies Supporting Labeled Indications

Placebo-controlled Safety and Efficacy Trials

SMART-1

Objective, Location, and Study Date

SMART-1 was a phase 3 trial designed to evaluate the endometrial safety of various doses of CE/BZA [4] and to evaluate the effects of CE/BZA on BMD [5]. Recruitment for the study was conducted between April 3, 2002 and December 31, 2003 at 94 sites in the United States, Europe, and Brazil [4].

Trial Design, Randomization, and Blinding Procedures

SMART-1 was a 2-year, outpatient, randomized, double-blind, placebo- and active-controlled, phase 3 study. Subjects were randomized to 1 of 8 treatment groups (see next section) [4].

Setting and Primary Inclusion/Exclusion Criteria

Inclusion Criteria [4]

- Generally healthy postmenopausal women (completed LMP ≥ 1 year before screening with serum FSH ≥ 30 mIU/mL and 17β -estradiol ≤ 50 pg/mL)
- Aged 40 to 75 years
- Intact uterus
- BMI ≤ 32.2 kg/m²
- No evidence of endometrial hyperplasia at screening

Exclusion Criteria [4]

- History or presence of estrogen-dependent neoplasia; thromboembolic disease, cerebrovascular event, or ischemic heart disease
- History of breast or gynecologic cancer
- Use of HT or SERM-containing medications within 8 weeks of screening

Women enrolled in Osteoporosis Prevention Substudy I were >5 years from LMP, had a screening lumbar spine or total hip BMD T-score between –1 and –2.5 (inclusive), and ≥1 additional risk factor for osteoporosis. Women enrolled in Osteoporosis Prevention Substudy II were 1 to 5 years from LMP with ≥1 risk factor for osteoporosis. Women with lumbar spine or total hip BMD >2.5 standard deviations (SD) below normal or a history of osteoporosis-related fractures were excluded [5].

Women were retrospectively selected from the main study to participate in the ancillary breast substudy if they completed 24 months of treatment, completed all scheduled evaluations, were ≥80% compliant, and had technically acceptable mammograms (original films) at baseline and Month 24 [8].

Treatment: Dosage Regimens, Washout Period, etc

Subjects were randomly allocated to 1 of 8 treatment groups: BZA (10, 20, or 40 mg) each combined with CE (0.45 or 0.625 mg), raloxifene 60 mg, or placebo. Subjects were to take 1 tablet orally at approximately the same time each day for 2 years [4].

Clinical Outcome Measures*Primary Efficacy Endpoints*

- Incidence of endometrial hyperplasia at Month 12 via endometrial biopsy (main study) [4]
- Lumbar spine BMD at Month 24 (Osteoporosis Prevention Substudies I and II) [5]

Secondary Efficacy Endpoints

- Incidence of endometrial hyperplasia at Months 6 and 24 [4]
- Hip and lumbar spine BMD measurements at Months 6, 12, 18, and 24 [5]
- Effects on VMS and VVA [6]
- Amenorrhea/bleeding profile [7]
- Breast pain [6]

Other Outcome Measures

- Breast density (Study 4000 ancillary substudy) [8]
- Sleep parameters [9]
- QOL (MENQOL) [10]
- Safety [6]

Subject Characteristics and Disposition

Demographic and baseline characteristics are provided in **Table 3.2**.

Table 3.2. Demographic and Baseline Characteristics for the SMART-1 Trial [6]

Characteristic	CE 0.45 mg/BZA 20 mg (n = 433)	Placebo (n = 427)
Age, y (%)	56.22 (5.80)	56.48 (6.04)
Ethnic origin, n (%) [*]		
White	351 (81.06)	340 (79.63)
Black	54 (12.47)	66 (15.46)
Hispanic	20 (4.62)	15 (3.51)
Other	8 (1.84)	6 (1.40)
BMI, kg/m ²	25.97 (3.45)	25.94 [†] (3.54)
Years since LMP	8.11 (5.70)	8.36 (5.78)

Values are mean (SD) unless otherwise noted.

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; BMI, body mass index; LMP, last menstrual period.

^{*}Percentages may not total 100.0% due to rounding.

[†]n = 426.

The discontinuation rate for the CE 0.45-mg/BZA 20-mg group was 29.8%; for the placebo group it was 35.4%.

Results

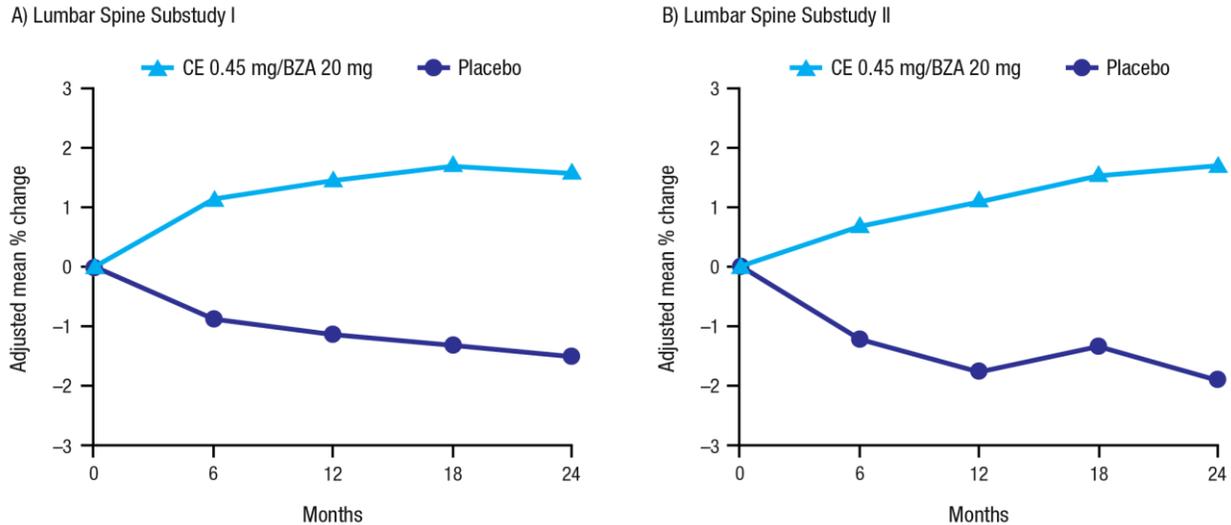
Endometrial Safety [4]

No endometrial hyperplasia was observed with CE 0.45 mg/BZA 20 mg or placebo at 12 months (primary endpoint); at Month 24, the difference from placebo \pm standard error (SE) in endometrial hyperplasia rate for CE 0.45 mg/BZA 20 mg was 0.34 ± 0.34 (95% confidence interval [CI], 0.33-1.01). The increase from baseline in endometrial thickness with CE 0.45 mg/BZA 20 mg was <1 mm and not significantly different from placebo at Month 12 or 24.

Effects on Bone [5]

In the Osteoporosis Prevention I and II Substudies, CE 0.45 mg/BZA 20 mg significantly increased lumbar spine and total hip BMD from baseline to all time points compared with decreases with placebo ($P < 0.05$; **Figure 3.1**). Bone turnover markers significantly decreased with CE 0.45 mg/BZA 20 mg compared with placebo at all time points ($P < 0.001$).

Figure 3.1. Adjusted mean percent change from baseline in lumbar spine BMD at Months 6, 12, 18, and 24 for CE 0.45 mg/BZA 20 mg compared with placebo in Osteoporosis Substudies I (A) and II (B). [5] Reprinted from *Fertility and Sterility*, Volume 92, Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G, Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women, pp. 1045-52, Copyright 2009, with permission from Elsevier.



$P < 0.01$ vs baseline for all time points and $P < 0.001$ vs placebo at all time points in both substudies. BMD, bone mineral density; CE, conjugated estrogens; BZA, bazedoxifene.

Effects on VMS [6]

CE 0.45 mg/BZA 20 mg significantly reduced the frequency ($P < 0.05$ for Weeks 5-12) and severity ($P < 0.001$ at Week 12) of hot flushes compared with placebo.

Vaginal Bleeding/Amenorrhea [7]

Rates of cumulative amenorrhea and bleeding/spotting were similar for CE 0.45 mg/BZA 20 mg compared with placebo.

Safety [6]

Incidences of adverse events (AEs; including VTEs and cardiovascular AEs) and breast pain were similar between the CE/BZA and placebo groups [6]. The majority of treatment-emergent AEs (TEAEs) were mild to moderate in severity and not considered related to study drug. A summary of the safety profile of CE/BZA is shown in **Table 3.3**.

Table 3.3. Summary of the Safety Profile and TEAEs ($\geq 10\%$) in the SMART-1 Trial [6]

Event	CE 0.45 mg/BZA 20 mg	CE 0.625 mg/BZA 20 mg	Placebo
	(n = 433) n, (%)	(n = 414) n, (%)	(n = 427) n, (%)
Any AE	401 (92.6)	382 (92.3)	392 (91.8)
Any serious AE	26 (6.0)	23 (5.6)	34 (8.0)
Any TEAE	401 (92.6)	382 (92.3)	392 (91.8)
Infections and infestations	276 (63.7)	252 (60.9)	254 (59.5)
Headache	135 (31.2)	129 (31.2)	117 (27.4)
Back pain	106 (24.5)	107 (25.8)	86 (20.1)
Arthralgia	101 (23.3)	110 (26.6)	112 (26.2)
Influenza	97 (22.4)	78 (18.8)	90 (21.1)
Nasopharyngitis	79 (18.2)	77 (18.6)	66 (15.5)
Pain in extremity	70 (16.2)	60 (14.5)	63 (14.8)
Abdominal pain	54 (12.5)	39 (9.4)	32 (7.5)
Myalgia	53 (12.2)	61 (14.7)	58 (13.6)
Upper respiratory infection	52 (12.0)	42 (10.1)	47 (11.0)
Abdominal pain upper	51 (11.8)	50 (12.1)	31 (7.3)
Pharyngolaryngeal pain	48 (11.1)	40 (9.7)	37 (8.7)
Muscle spasms*	47 (10.9)	30 (7.2)	22 (5.2)
Nausea	46 (10.6)	30 (7.2)	23 (5.4)
Diarrhea	44 (10.2)	28 (6.8)	26 (6.1)
Urinary tract infection	40 (9.2)	42 (10.1)	35 (8.2)
Insomnia	38 (8.8)	23 (5.6)	48 (11.2)
Sinusitis	27 (6.2)	43 (10.4)	41 (9.6)

TEAE, treatment-emergent adverse event; SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; AE, adverse event.

* $P < 0.05$ overall.

Other Outcome Measures

Effects on Breast Density [8]

The mean (SD) percent change in breast density from baseline to Month 24 for CE 0.45 mg/BZA 20 mg (-0.39 [1.75]%) was similar to that for placebo (-0.42 [1.72]%).

Effects on Sleep [9]

CE 0.45 mg/BZA 20 mg was associated with significant improvements in mean quality of sleep ($P \leq 0.01$), time to fall asleep ($P \leq 0.01$), and minutes slept ($P < 0.05$) compared with placebo.

Effects on QOL [10]

CE 0.45 mg/BZA 20 mg significantly improved total MENQOL score and vasomotor function score compared with placebo ($P < 0.001$).

Exploratory BMD Data [84]

In a post hoc exploratory analysis, women with higher baseline bone marker levels (osteocalcin and C-telopeptide) also had larger increases in lumbar spine BMD after 2 years of treatment with CE 0.45

mg/BZA 20 mg. In addition, early reductions in hot flush score at 12 weeks were correlated with long-term increases in lumbar spine (-0.31 ; $P = 0.006$) and total hip (-0.23 ; $P = 0.044$) BMD.

Generalizability of Population Treated and Study Limitations (As Stated by Authors)

Because the **SMART-1 trial** was conducted in a wide age range (40-75 years) and menopausal symptoms were generally experienced only by those in the younger age range, the number of subjects available for evaluation of VMS was limited [6]. The study was not powered to detect small differences in cardiovascular safety endpoints [6].

Publication Citations/References Used Including Funding Source of the Study

Pickar JH, Yeh I, Bachmann GA, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. *Fertil Steril*. 2009;92(3):1018-1024. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril*. 2009;92(3):1045-1052. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

Lobo RA, Pinkerton JV, Gass MLS, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. *Fertil Steril*. 2009;92(3):1025-1038. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. *Fertil Steril*. 2009;92(3):1039-1044. Funding: sponsored by Wyeth Research, Collegeville, PA (now Pfizer).

Harvey JA, Pinkerton JV, Baracat EC, Shi H, Chines AA, Mirkin S. Breast density changes in a randomized controlled trial evaluating bazedoxifene/conjugated estrogens. *Menopause*. 2013;20(2):138-145. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

Pinkerton JV, Chines AA, Racketta J, Mirkin S. Bazedoxifene/conjugated estrogens (BZA/CE): effect on sleep parameters in postmenopausal women. *Menopause*. 2010;17:1237-8. Abstract P-53. Funding: sponsored by Pfizer Inc.

Pinkerton JV, Chines AA, Racketta J, Mirkin S. Menopause-related quality of life and satisfaction in postmenopausal women treated with bazedoxifene/conjugated estrogens (BZA/CE). *Menopause*. 2010;17:1219. Abstract S-12. Funding: sponsored by Pfizer Inc.

Gallagher JC, Shi H, Mirkin S, Chines AA. Changes in bone mineral density are correlated with bone markers and reductions in hot flush severity in postmenopausal women treated with bazedoxifene/conjugated estrogens. *Menopause*. 2013[Epub before print]. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

SMART-2**Objective, Location, and Study Date**

SMART-2 was a phase 3 trial designed to assess the safety and efficacy of CE/BZA for the treatment of moderate to severe VMS associated with menopause. The study was conducted between April 2002 and January 2006 at 43 sites in the United States [11].

Trial Design, Randomization, and Blinding Procedures

SMART-2 was a 12-week, outpatient, randomized, double-blind, placebo-controlled, phase 3 study that randomly assigned subjects to 3 treatment groups following a 2:2:1 ratio (see next section) [11].

Setting and Primary Inclusion/Exclusion Criteria*Inclusion Criteria [11]*

- Healthy, postmenopausal women (≥ 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH > 40 mIU/mL)
- Aged 40 to 65 years
- BMI ≤ 34.0 kg/m²
- Seeking treatment for hot flushes and having experienced ≥ 7 moderate to severe hot flushes per day or ≥ 50 per week at screening

Exclusion Criteria [11]

- History or presence of endometrial hyperplasia, estrogen-dependent neoplasia, thromboembolic disease, cerebrovascular event, or ischemic heart disease
- History of breast or gynecologic cancer
- Use of HT or SERM-containing medications within 8 weeks of screening

Treatment: Dosage Regimens, Washout Period, etc

Subjects were randomly assigned in a 2:2:1 ratio to CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, or placebo. Subjects were to take 1 tablet orally at approximately the same time each day for 12 weeks [11].

Clinical Outcome Measures*Primary Efficacy Endpoint*

- Change from baseline in mean daily number of moderate to severe hot flushes [11]
- Mean severity of hot flushes at Weeks 4 and 12 [11]

Secondary Efficacy Endpoints

- Percentage of responders ($\geq 50\%$ or $\geq 75\%$ reduction in hot flush number) [11]
- Breast pain [11]
- Sleep parameters (Medical Outcomes Study [MOS] sleep scale) [11]
- QOL (MENQOL) [11]

Other Outcome Measures

- Satisfaction with treatment (MS-TSQ) [12]
- Safety [11]

Subject Characteristics and Disposition

Demographic and baseline characteristics are provided in **Table 3.4**.

Table 3.4. Demographic and Baseline Characteristics for the SMART-2 Trial [11]

Characteristic	CE 0.45 mg/BZA 20 mg (n = 127)	Placebo (n = 63)
Age, y (%)	53.57 (4.82)	53.62 (5.31)
Race, n (%)		
White	112 (88.19)	53 (84.13)
Black	11 (8.66)	7 (11.11)
Other	4 (3.15)	3 (4.76)
BMI, kg/m ²	26.37 (3.91)	26.03 (4.19)
Years since LMP	4.69 (4.18)	4.84 (4.59)

Values are mean (SD) unless otherwise noted.

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; BMI, body mass index; LMP, last menstrual period.

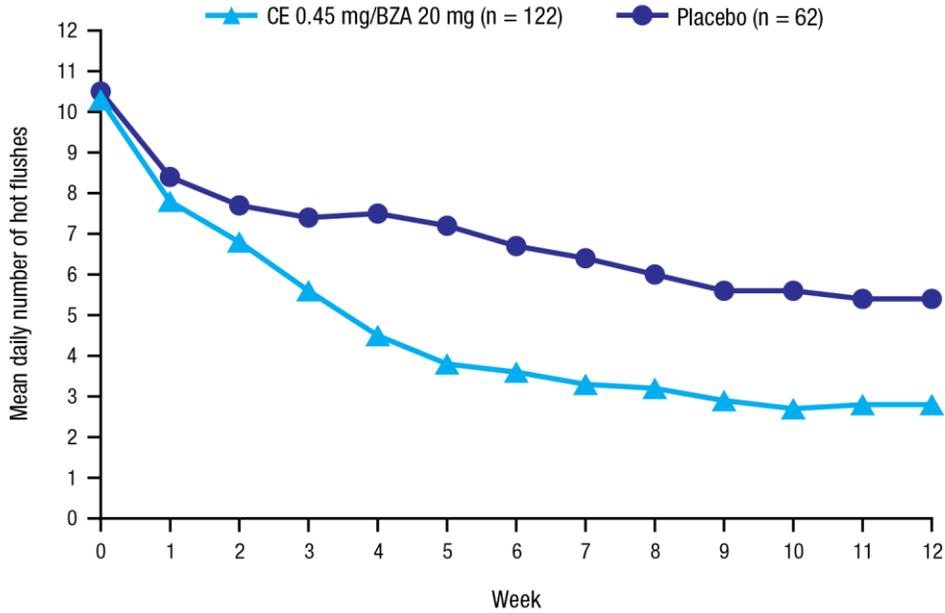
In the CE 0.45-mg/BZA 20-mg group, 14 of 127 subjects (11.0%) discontinued; in the placebo group, 10 of 63 subjects (15.9%) discontinued.

Results

Effects on VMS [11]

CE 0.45 mg/BZA 20 mg significantly reduced the mean daily number of moderate and severe hot flushes from baseline compared with placebo, with significant differences observed at Week 3 ($P = 0.008$) and maintained through Week 12 ($P < 0.01$; **Figure 3.2**). At Week 12, CE 0.45 mg/BZA 20 mg reduced the mean daily number of hot flushes from baseline by 74% compared with 51% for placebo.

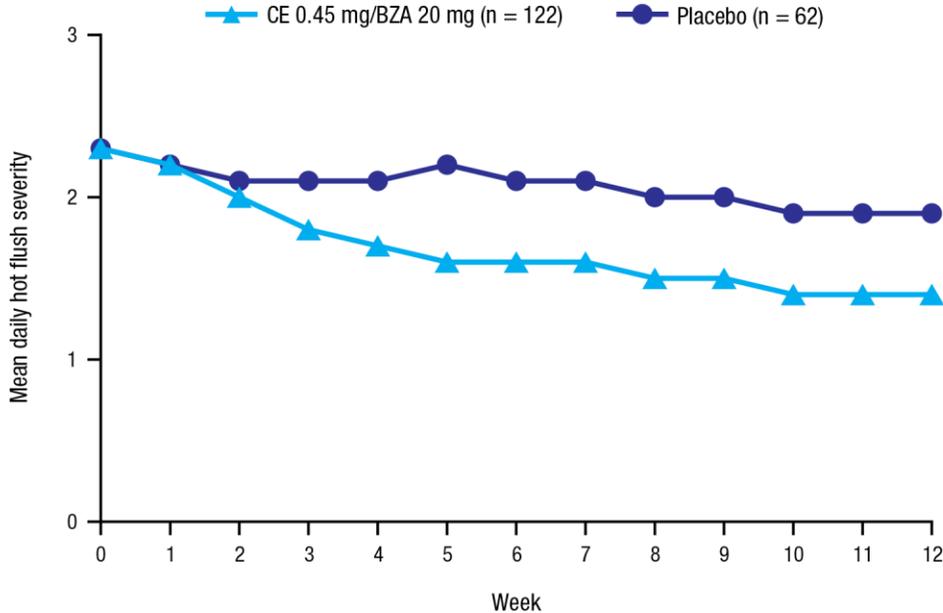
Figure 3.2. Mean daily number of hot flushes with up to 12 weeks of treatment with CE 0.45 mg/BZA 20 mg or placebo [11]. Reprinted with permission from Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause*. 2009;16(6):1116-24.



$P < 0.01$ for CE 0.45 mg/BZA 20 mg compared with placebo during Weeks 3 through 12. CE, conjugated estrogens; BZA, bazedoxifene.

CE 0.45 mg/BZA 20 mg significantly reduced the mean daily severity of hot flushes from baseline compared with placebo, with significant differences observed during Weeks 3 through 12 ($P < 0.001$) (Figure 3.3).

Figure 3.3. Mean daily severity score of hot flushes with up to 12 weeks of treatment with CE 0.45 mg/BZA 20 mg or placebo [11]. Reprinted with permission from Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause*. 2009;16(6):1116-24.



$P < 0.001$ for CE 0.45 mg/BZA 20 mg compared with placebo for Weeks 3 to 12. Mean daily severity score = $(\text{[# mild hot flushes} \times 1] + \text{[# moderate hot flushes} \times 2] + \text{[# severe hot flushes} \times 3])$. CE, conjugated estrogens; BZA, bazedoxifene.

Significantly more women had a $\geq 75\%$ (61% vs 27%, respectively; $P < 0.001$) and a $\geq 50\%$ (83% vs 52%; $P < 0.001$) decrease in the number of moderate and severe hot flushes with CE 0.45 mg/BZA 20 mg compared with placebo at Week 12.

Effects on Sleep [12]

CE 0.45 mg/BZA 20 mg significantly improved MOS sleep scale scores for time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II compared with placebo at Week 12 ($P < 0.001$). Reduction in hot flush frequency was significantly associated with improvements in sleep parameters based on linear regression and responder analyses ($P < 0.05$).

Effects on QOL [12]

CE 0.45 mg/BZA 20 mg showed significantly greater improvements in vasomotor function and total MENQOL score at Week 12 ($P < 0.001$) compared with placebo.

Safety [11]

Overall, there were no significant differences among CE/BZA and placebo groups in the number of participants reporting any TEAE, including those reporting at least 1 day of breast pain, or the incidence of AEs resulting in study discontinuation. No participants reported any VTEs, superficial venous

thrombosis, or cerebrovascular events. TEAEs reported by at least 5% of participants are summarized in **Table 3.5**.

Table 3.5. TEAEs in ≥5% of Participants in the SMART-2 Trial [11]

Event	CE 0.45 mg/BZA 20 mg	CE 0.625 mg/BZA 20 mg	Placebo
	(n = 127) n, (%)	(n = 128) n, (%)	(n = 63) n, (%)
Any AE	77 (60.6)	86 (67.2)	46 (73.0)
Headache	20 (15.7)	20 (15.6)	12 (19.0)
Infection	10 (7.9)	10 (7.8)	7 (11.1)
Pain	10 (7.9)	8 (6.3)	7 (11.1)
Arthralgia	10 (7.9)	7 (5.5)	7 (11.1)
Back pain	9 (7.1)	9 (7.0)	4 (6.3)
Accidental injury	7 (5.5)	9 (7.0)	2 (3.2)
Nausea	6 (4.7)	7 (5.5)	2 (3.2)
Myalgia	4 (3.1)	2 (1.6)	4 (6.3)
Dyspepsia	3 (2.4)	7 (5.5)	3 (4.8)
Insomnia	2 (1.6)	5 (3.9)	5 (7.9)
Sinusitis*	2 (1.6)	0	5 (7.9)
Upper respiratory infection	1 (0.8)	5 (3.9)	4 (6.3)

TEAE, treatment-emergent adverse event; SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; AE, adverse event.

* $P < 0.01$ by the χ^2 test.

Other Outcome Measures

Results of the MS-TSQ showed that subjects treated with CE 0.45 mg/BZA 20 mg compared with placebo had significantly greater overall satisfaction with treatment, and significantly greater satisfaction in ability to control hot flushes during the day and night, effect on quality of sleep, effect on mood or emotions, effect on ability to concentrate, and satisfaction with tolerability to side effects ($P < 0.05$ for all) [12].

In a secondary analysis, CE 0.45 mg/BZA 20 mg significantly increased both the number of hot flush symptom-free days from Weeks 3 to 12 ($P < 0.05$) and the proportion of women without moderate to severe hot flushes at Week 12 ($P < 0.01$) compared with placebo [13].

Study Limitations (As Stated by Authors)

Because of the low incidence of VTE, this study enrolled too few participants for too short a duration to adequately assess the risk of these events with CE/BZA [11].

Publication Citations/References Used Including Funding Source of the Study

Pinkerton JV, Utian WH, Constantine G, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause*. 2009;16(6):1116-1124. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

Utian WH, Yu H, Bobula J, Mirkin S, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. *Maturitas*. 2009;63(4):329-335. Funding: supported by Wyeth Research, Collegeville, Pennsylvania (now Pfizer).

Yu H, Racketa J, Chines AA, Mirkin S. Hot flush symptom-free days with bazedoxifene/conjugated estrogens in postmenopausal women. *Climacteric*. 2013;16:252-257. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

SMART-3

Objective, Location, and Study Date

SMART-3 was a phase 3 study designed to assess the efficacy and safety of CE/BZA for the treatment of moderate to severe vulvar/vaginal atrophy (VVA) associated with menopause. The study was conducted between October 2005 and March 2007 at 66 sites in the United States [14].

Trial Design, Randomization, and Blinding Procedures

SMART-3 was a 12-week, randomized, double-blind, placebo-controlled, comparator phase 3 study that randomly assigned subjects to 4 treatment groups following a 2:2:1:1 ratio (see next section) [14].

Setting and Primary Inclusion/Exclusion Criteria

Inclusion Criteria [14]

- Healthy, postmenopausal women (≥ 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH >40 mIU/mL)
- Aged 40 to 65 years
- Intact uterus
- BMI ≤ 34.0 kg/m²
- Vaginal cytological smear showing vaginal pH >5.0 and $\leq 5\%$ superficial cells, and ≥ 1 bothersome moderate to severe symptom of VVA at screening

Exclusion Criteria [14]

- History or presence of endometrial hyperplasia, estrogen-dependent neoplasia, thromboembolic disease, cerebrovascular event, or ischemic heart disease
- History of breast or gynecologic cancer
- Use of HT or SERM-containing medications within 8 weeks of screening

Treatment: Dosage Regimens, Washout Period, etc

Subjects were randomly assigned in a 2:2:1:1 ratio to CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, BZA 20 mg, or placebo. Subjects were to take 1 tablet orally at approximately the same time each day for 12 weeks [14].

Clinical Outcome Measures

Primary Efficacy Endpoints [14]

- Severity of most bothersome VVA symptom at Week 12
- Vaginal pH at Week 12
- Proportion of vaginal superficial cells at Week 12
- Proportion of vaginal parabasal cells at Week 12

Secondary Efficacy Endpoints [14]

- Individual VVA symptoms (eg, vaginal dryness, itching, dyspareunia)
- Assessment of 4 co-primary endpoints at Week 4

Other Outcome Measures [14]

- Sexual function (Arizona Sexual Experiences Scale [ASEX])
- QOL (MENQOL)
- Satisfaction with treatment (MS-TSQ)
- Safety

Patient Characteristics and Disposition

Demographic and baseline characteristics are provided in **Table 3.6**.

Table 3.6. Demographic and Baseline Characteristics for the SMART-3 Trial [14]

Characteristic	CE 0.45 mg/BZA 20 mg (n = 219)	BZA 20 mg (n = 110)	Placebo (n = 105)
Age, y	56.43 (4.74)	56.37 (4.49)	56.10 (4.15)
Race, n (%) [*]			
White	202 (92.2)	103 (93.6)	96 (91.4)
Black	6 (2.7)	4 (3.6)	2 (1.9)
Other	11 (5.0)	3 (2.7)	7 (6.7)
BMI, kg/m ²	25.38 (3.80)	25.28 (3.86)	25.74 (4.09)
Years since LMP	7.53 (4.92)	7.81 (4.74)	7.18 (4.24)
Type of menopause, n (%)			
Natural	219 (100)	110 (100)	105 (100)

Values are mean (SD) unless otherwise noted.

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; BMI, body mass index; LMP, last menstrual period.

^{*}Percentages may not total 100.0% because of rounding.

Discontinuation rates for the CE 0.45-mg/BZA 20-mg, BZA 20-mg, and placebo groups were 14/219 (6.4%), 11/110 (10.0%), and 8/105 (7.6%), respectively [14].

Results*Efficacy*

CE/BZA is not indicated for the treatment of VVA and, thus, results for these efficacy endpoints will not be presented in this document.

Safety [14]

The incidence of TEAEs was similar across treatment groups, and most events were mild to moderate in severity. There were no significant differences between groups in the rate of discontinuations due to AEs. The incidence of gynecologic TEAEs (eg, breast pain, ovarian cysts, and vaginal bleeding) was not significantly different with CE/BZA compared with placebo, except for a higher incidence of vaginitis with both doses of CE/BZA compared with placebo. TEAEs reported by $\geq 5\%$ of women in any treatment group are summarized in **Table 3.7**.

Table 3.7. TEAEs in $\geq 5\%$ of Participants in the SMART-3 Trial [14]

Event	CE 0.45 mg/BZA 20 mg (n = 219) n, (%)	CE 0.625 mg/BZA 20 mg (n = 218) n, (%)	BZA 20 mg (n = 110) n, (%)	Placebo (n = 105) n, (%)
Any AE	164 (74.9)	175 (80.3)	90 (81.8)	75 (71.4)
Headache	41 (18.7)	49 (22.5)	22 (20.0)	21 (20.0)
Pain	25 (11.4)	20 (9.2)	7 (6.4)	17 (16.2)
Back pain	21 (9.6)	26 (11.9)	15 (13.6)	8 (7.6)
Vasodilatation*	17 (7.8)	10 (4.6)	17 (5.5)	4 (3.8)
Nausea	14 (6.4)	13 (6.0)	5 (4.5)	4 (3.8)
Arthralgia	14 (6.4)	16 (7.3)	13 (11.8)	6 (5.7)
Myalgia	13 (5.9)	9 (4.1)	3 (2.7)	5 (4.8)
Infection	12 (5.5)	22 (10.1)	9 (8.2)	11 (10.5)
Diarrhea	12 (5.5)	7 (3.2)	5 (4.5)	7 (6.7)
Dyspepsia	12 (5.5)	12 (5.5)	7 (6.4)	5 (4.8)
Pharyngitis	11 (5.0)	18 (8.3)	8 (7.3)	5 (4.8)
Insomnia	10 (4.6)	10 (4.6)	9 (8.2)	3 (2.9)
Accidental injury*	7 (3.2)	11 (5.0)	12 (10.9)	2 (1.9)
Abdominal distension	7 (3.2)	5 (2.3)	9 (8.2)	4 (3.8)
Migraine [†]	6 (2.7)	2 (0.9)	2 (1.8)	7 (6.7)
Abdominal pain	5 (2.3)	10 (4.6)	5 (4.5)	6 (5.7)
Leg cramps	4 (1.8)	11 (5.0)	2 (1.8)	2 (1.9)
Vaginitis [†]	4 (1.8)	12 (5.5)	7 (6.4)	1 (1.0)
Constipation	3 (1.4)	12 (5.5)	7 (6.4)	3 (2.9)

TEAE, treatment-emergent adverse event; SMART, Selective Estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; AE, adverse event.

* $P < 0.01$ for overall P values from χ^2 analysis.

[†] $P < 0.05$ for overall P values from χ^2 analysis.

Other Outcome Measures*Effects on Sexual Function [15]*

CE 0.45 mg/BZA 20 mg improved sexual function at Week 12 based on ASEX scores, but there was no significant difference in total ASEX score or scores for ease of arousal, ease of orgasm, satisfaction with orgasm, or sex drive with CE/BZA compared with placebo. CE 0.45 mg/BZA 20 mg significantly improved ease of lubrication score from baseline to Week 12 compared with placebo ($P < 0.05$).

Effects on QOL [15]

CE 0.45 mg/BZA 20 mg significantly improved vasomotor function, sexual function, and total scores on the MENQOL questionnaire at Week 12 compared with placebo ($P \leq 0.001$).

Satisfaction With Treatment [15]

Subjects receiving CE 0.45 mg/BZA 20 mg had significantly greater overall satisfaction on the MS-TSQ compared with placebo ($P < 0.05$). CE 0.45 mg/BZA 20 mg was associated with significantly greater satisfaction compared with placebo for control of hot flushes during the day or night, effect on quality of sleep, and effect on mood or emotions ($P < 0.001$ for all).

Publication Citations/References Used Including Funding Source of the Study

Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. *Menopause*. 2010;17(2):281-289. Funding supported by Wyeth Research, Collegeville, PA (now Pfizer).

Bachmann GA, Bobula J, Mirkin S. Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. *Climacteric*. 2010;13(2):132-140. Funding supported by Wyeth Research, Collegeville, PA (now Pfizer).

SMART-4**Objective, Location, and Study Date**

SMART-4 was a phase 3 study designed to examine the effects of CE/BZA on the incidence of endometrial hyperplasia and the prevention of postmenopausal osteoporosis (osteoporosis substudy). The study was conducted between September 2005 and September 2008 at 62 sites in the United States and 2 sites in Argentina [3].

Trial Design, Randomization, and Blinding Procedures

SMART-4 was a 1-year, multicenter, double-blind, randomized, placebo- and active-controlled, phase 3 study that randomly assigned subjects to 4 treatment groups at a ratio of 2:2:1:1 (see next section) [3].

Setting and Primary Inclusion/Exclusion Criteria*Inclusion Criteria [3]*

- Healthy, postmenopausal women (≥ 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH > 40 mIU/mL)
- Aged 40 to < 65 years
- Intact uterus
- BMI ≤ 34.0 kg/m²
- Acceptable endometrial biopsy report at screening

Exclusion Criteria [3]

- Use of HT-containing medications within 8 weeks of screening
- History or active presence of clinically important medical disease (eg, endometrial hyperplasia, thromboembolic disorders, cardiac disease)

Subjects were eligible for the osteoporosis substudy if they were ≤ 5 years since LMP at screening and had 2 evaluable BMD scans of the lumbar spine and total hip that differed by $< 5.0\%$ and $< 7.5\%$, respectively. Subjects with lumbar spine or total hip T-scores < -2.5 at screening or with current/history of osteoporosis or fragility fracture were excluded from the substudy [3].

Treatment: Dosage Regimens, Washout Period, etc

Subjects were randomly assigned in a 2:2:1:1 ratio to CE 0.45 mg/BZA 20 mg, CE 0.625 mg/BZA 20 mg, CE 0.45 mg/MPA 1.5 mg, or placebo daily for 1 year. **SMART-4** used 2 formulations of CE/BZA, neither of which had been used in the **SMART-1 trial**. One of these formulations, which was administered to the majority of subjects during Year 1, was shown to have decreased bioavailability of the BZA component (approximately 18% lower) compared with the formulation used in the **SMART-1 trial** [3]. Because the reduced bioavailability of BZA in the formulation used in this trial led to insufficient endometrial protection with CE/BZA, efficacy and endometrial safety results with CE/BZA will not be presented for **SMART-4**.

Clinical Outcome Measures*Primary Efficacy Endpoints [3]*

- Incidence of endometrial hyperplasia at 1 year via endometrial biopsy (main study)
- Mean percent change from baseline in lumbar spine BMD at 1 year (osteoporosis substudy)

Secondary Efficacy Endpoints [3]

- Cumulative and noncumulative amenorrhea rates
- Breast pain
- Mean percent change from baseline in hip BMD and bone metabolism profile

Other Outcome Measures [3]

- Safety

Patient Characteristics and Disposition

Demographic and baseline characteristics are provided in **Table 3.8**.

Table 3.8. Demographic and Baseline Characteristics for the SMART-4 Trial [3]

Characteristic	CE 0.45 mg/BZA 20 mg (n = 361)	CE 0.45 mg/MPA 1.5 mg (n = 179)	Placebo (n = 172)
Age, y	54.6 (4.7)	54.3 (4.6)	54.2 (4.6)
Race, n (%) [*]			
White	340 (94.2)	163 (91.1)	160 (93.0)
Black	12 (3.3)	8 (4.5)	7 (4.1)
Other	9 (2.5)	8 (4.5)	5 (2.9)
BMI, kg/m ²	26.2 (3.8)	26.0 (3.8)	26.3 (3.9)
Year since LMP	5.4 (4.7)	5.4 (4.9)	5.4 (4.1)

Values are mean (SD) unless otherwise noted.

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; MPA, medroxyprogesterone acetate; BMI, body mass index; LMP, last menstrual period.

^{*}Percentages may not total 100.0% because of rounding.

Rates of study discontinuation were as follows: CE 0.45 mg/BZA 20 mg, 74/361 (20.5%); CE 0.45 mg/MPA 1.5 mg, 47/179 (26.2%); placebo, 30/172 (17.4)% [3].

Results

As previously mentioned, efficacy and endometrial safety results with CE/BZA will not be presented because reduced bioavailability of BZA in the formulation used in this trial led to insufficient endometrial protection with CE/BZA.

Safety [3]

There were no significant differences among groups in overall incidences of AEs, TEAEs, serious AEs, and study discontinuations due to AEs (**Table 3.9**). Significantly lower rates of study discontinuations due to bleeding-related AEs were reported with CE/BZA compared with CE/MPA ($P < 0.01$ for all). Incidences of AEs of special interest, including selected cardiac events, cerebrovascular events, and reproductive tract and breast-related AEs were similar among groups.

Table 3.9. Summary of Safety Profile From the SMART-4 Trial* [3]

Event	CE 0.45 mg/ BZA 20 mg (n = 361) n, (%)	CE 0.625 mg/ BZA 20 mg (n = 349) n, (%)	CE 0.45 mg/ MPA 1.5 mg (n = 179) n, (%)	Placebo (n = 172) n, (%)
Any AE	308 (85.3)	299 (85.7)	160 (89.4)	147 (85.5)
Any TEAE	298 (82.5)	281 (80.5)	151 (84.4)	139 (80.8)
Any serious AE	15 (4.2)	11 (3.2)	4 (2.2)	5 (2.9)
Discontinuations due to AEs	30 (8.3)	25 (7.2)	23 (12.8)	14 (8.1)
Death	0	0	1 (0.6)	0
Selected AEs				
VTE	2 (0.6)	0	0	0
Angina pectoris	1 (0.3)	0	1 (0.6)	0
Coronary artery disease	0	1 (0.3)	0	0
Cerebrovascular events	1 (0.3)	0	0	0
Breast cyst	1 (0.3)	0	1 (1.6)	2 (1.2)
Fibrocystic breast disease	2 (0.6)	1 (0.3)	0	0
Uterine polyp	1 (0.3)	1 (0.3)	1 (0.6)	0
Ovarian cyst	1 (0.3)	1 (0.3)	1 (0.6)	0

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; MPA, medroxyprogesterone acetate; AE, adverse event; TEAE, treatment-emergent adverse event, VTE, venous thromboembolism.

*Mirkin S, Komm BS, Pan K, Chines AA, *Climacteric*, 2013;16(3):338-46, copyright © 2013, Informa Healthcare. Reproduced with permission of Informa Healthcare.

Publication Citation/Reference Used Including Funding Source of the Study

Mirkin S, Komm BS, Pan K, Chines AA. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. *Climacteric*. 2013;16(3):338-346. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

SMART-5

Objective, Location, and Study Date

SMART-5 was a phase 3 study designed to evaluate the endometrial safety of CE/BZA and effects on BMD compared with BZA alone, CE/MPA, and placebo. The study was conducted between January 2009 and February 2011 at 166 sites globally [86].

Trial Design, Randomization, and Blinding Procedures

SMART-5 was a 1-year, multicenter, international, randomized, double-blind, placebo- and active-controlled, phase 3 study that randomly assigned subjects to 5 treatment groups at a ratio of 2:2:1:1:2 (see next section) [86].

Setting and Primary Inclusion/Exclusion Criteria

Inclusion Criteria [86]

- Healthy, postmenopausal women
- Aged 40 to 65 years
- Intact uterus
- BMI ≤ 34.0 kg/m²
- Acceptable endometrial biopsy report at screening
- Seeking treatment for menopausal symptoms

Exclusion Criteria [86]

- Use of HT or SERM-containing medications within 8 weeks of screening
- History or active presence of clinically important medical disease

Subjects were eligible for the osteoporosis substudy if they were ≤ 5 years since LMP and had 2 evaluable BMD scans at screening of the lumbar spine and total hip that differed by $< 5.0\%$ and $< 7.5\%$, respectively. Subjects with lumbar spine or total hip T-scores < -2.5 at screening or with current/history of osteoporosis or low-impact traumatic fracture were excluded from the substudy [86].

The sleep/QOL substudy enrolled a subset of women from **SMART-5** who had bothersome moderate to severe VMS at baseline [86].

Women with a technically acceptable digital mammogram at screening were eligible for the breast density substudy [16].

Treatment: Dosage Regimens, Washout Period, etc

Subjects were randomly assigned in a 2:2:1:1:2 ratio to CE 0.45 mg/BZA 20 mg, CE 0.6256 mg/BZA 20 mg, BZA 20 mg, CE 0.45 mg/MPA 1.5 mg, or placebo daily for 1 year [86].

Clinical Outcome Measures [86]*Primary Efficacy Endpoints*

- Incidence of endometrial hyperplasia at 12 months via endometrial biopsy (main study)
- Percent change from baseline in lumbar spine BMD at 12 months (osteoporosis substudy)
- Change from baseline in breast density at 12 months (breast density substudy) [16]

Secondary Efficacy Endpoints

- Cumulative amenorrhea rate
- Breast tenderness incidence
- Change from baseline in total hip BMD and bone turnover markers

Other Outcome Measures

- Sleep (MOS sleep scale, sleep/QOL substudy)
- QOL (MENQOL, sleep/QOL substudy)
- Safety

Patient Characteristics and Disposition

Demographic and baseline characteristics are provided in **Table 3.10**.

Table 3.10. Demographic and Baseline Characteristics for the SMART-5 Trial [86]

Characteristic	CE 0.45 mg/BZA 20 mg (n = 445)	BZA 20 mg (n = 230)	CE 0.45 mg/MPA 1.5 mg (n = 220)	Placebo (n = 474)
Age, y	54.4 (4.0)	54.1 (4.0)	54.2 (4.5)	54.2 (4.1)
Race, n (%) [*]				
White	397 (89.2)	207 (90.0)	193 (87.7)	426 (89.9)
Black	31 (7.0)	19 (8.3)	20 (9.1)	34 (7.2)
Other	17 (3.8)	4 (1.7)	7 (3.2)	14 (3.0)
BMI, kg/m ²	25.8 (3.8)	26.5 (3.9)	26.2 (3.9)	26.0 (3.9)
Year since LMP	5.2 (4.5)	4.5 (3.8)	4.7 (3.8)	4.8 (4.2)

Values are mean (SD) unless otherwise noted.

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; MPA, medroxyprogesterone acetate; BMI, body mass index; LMP, last menstrual period.

^{*}Percentages may not total 100.0% because of rounding.

The rate of discontinuation for subjects treated with CE 0.45 mg/MPA 1.5 mg (61/220 [27.7%]) was significantly higher than for those given CE 0.45 mg/BZA 20 mg (88/445 [19.8%]), BZA 20 mg (45/230 [19.6%]), and placebo (91/474 [19.2%]); overall $P < 0.05$) [86].

Results

Endometrial Safety [86]

Rates of endometrial hyperplasia were <1% and similar for CE 0.45 mg/BZA 20 mg, BZA 20 mg, CE 0.45 mg/MPA 1.5 mg, and placebo (**Table 3.11**). CE 0.45 mg/BZA 20 mg ($P < 0.05$) and CE 0.45 mg/MPA 1.5 mg ($P < 0.001$) showed significantly greater increases from baseline in endometrial thickness compared with placebo. Incidence of proliferative endometrium was <1% and similar among groups.

Table 3.11. Summary of Selected Endometrial Safety Parameters at Month 12 From the SMART-5 Trial [86]

Parameter	CE 0.45 mg/ BZA 20 mg	BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo
Endometrial hyperplasia n/N (%) [*]	1/335 (0.30) [†]	0/169	0/149	1/354 (0.28) [‡]
Upper limit of 1-sided 95% CI	1.41	1.76	1.99	1.33
Adjusted change from baseline in endometrial thickness, mm				
Mean (SE)	0.17 (0.08) [§]	0.09 (0.11)	0.78 (0.12)	0.09 (0.08)
Increase from baseline >3 mm [¶]	10/384 (2.6)	3/195 (1.5)	9/181 (5.0)	12/405 (3.0)
Increase from baseline >5 mm [#]	4/384 (1.0)	0/195	5/181 (2.8)	2/405 (0.5)
Endometrial thickness >4 mm [#]	44/384 (11.5)	16/195 (8.2)	31/181 (17.1)	45/405 (11.1)
Endometrial thickness >8 mm	3/384 (0.8)	0/195	4/181 (2.2)	2/405 (0.5)
Proliferative endometrium n/N (%)	2/338 (0.59)	0/171	1/153 (0.65)	1/356 (0.28)

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; MPA, medroxyprogesterone acetate; CI, confidence interval; SE, standard error; EE, efficacy evaluable; ANCOVA, analysis of covariance.

^{*}Subjects in the EE population, consisting of randomized subjects who received ≥ 1 dose of study drug, did not have endometrial hyperplasia at baseline, had endometrial biopsies at screening and Month 12 or were diagnosed with endometrial hyperplasia before Month 12, and had no major protocol violations.

[†]Hyperplasia with atypia diagnosed by 1 of 3 independent pathologists.

[‡]Hyperplasia with atypia diagnosed by 1 of 2 independent pathologists.

[§] $P < 0.05$ vs placebo (ANCOVA).

^{||} $P < 0.001$ vs placebo (ANCOVA).

[¶]Overall $P < 0.01$ (chi-square test).

[#]Overall $P < 0.05$ (chi-square test).

Effects on Bone [86]

CE 0.45 mg/BZA 20 mg, BZA 20 mg, and CE 0.45 mg/MPA 1.5 mg significantly increased lumbar spine, total hip, and femoral neck BMD compared with placebo ($P < 0.01$ for all) and showed significantly greater decreases from baseline in serum bone turnover markers compared with placebo ($P < 0.01$ for all) at 12 months. There were no differences among groups in the incidence of fractures reported as AEs, although this study was not specifically powered to evaluate fracture incidence.

Vaginal Bleeding/Amenorrhea [86]

Rates of cumulative amenorrhea were similar for CE 0.45 mg/BZA 20 mg, BZA 20 mg, and placebo over 1 year of treatment and significantly higher than those for CE/MPA at all time points ($P < 0.001$).

Breast Tenderness [16]

Based on diary data, the percentage of subjects reporting at least 1 day of breast tenderness was similar for CE 0.45 mg/BZA 20 mg, BZA alone, and placebo but significantly lower than for CE/MPA ($P < 0.001$ vs placebo and $P < 0.01$ vs CE/BZA or BZA alone for all time periods).

Safety [86]

Incidences of AEs, TEAEs, and serious AEs were similar with CE/BZA and placebo; more subjects in the CE/MPA group discontinued the study due to AEs compared with other groups (**Table 3.12**). There were no differences among groups in rates of selected cardiac, cerebrovascular, or breast-related AEs. Incidence of bleeding-related AEs was similar with CE/BZA and placebo and significantly lower than with CE/MPA (overall $P < 0.001$).

Table 3.12. Overall Summary of Safety Parameters From the SMART-5 Trial [86]

Event	CE 0.45 mg/ BZA 20 mg (n = 445) n, (%)	CE 0.625 mg/ BZA 20 mg (n = 474) n, (%)	BZA 20 mg (n = 230) n, (%)	CE 0.45 mg/ MPA 1.5 mg (n = 220) n, (%)	Placebo (n = 474) n, (%)
Any AE	407 (91.5)	426 (89.9)	207 (90.0)	197 (89.5)	424 (89.5)
Any TEAE	375 (84.3)	404 (85.2)	194 (84.3)	187 (85.0)	392 (82.7)
Any serious AE	16 (3.6)	17 (3.6)	5 (2.2)	13 (5.9)	18 (3.8)
Discontinuations due to AEs*					
Any AE [†]	34 (7.6)	33 (7.0)	16 (7.0)	31 (14.1)	33 (7.0)
Breast tenderness [‡]	0	1 (0.2)	1 (0.4)	4 (1.8)	1 (0.2)
Pelvic pain [§]	0	0	0	3 (1.4)	0
Vaginal hemorrhage [§]	1 (0.2)	0	0	5 (2.3)	1 (0.2)
Deaths	0	0	0	0	1 (0.2)
Most common TEAEs [‡]					
Nasopharyngitis [†]	80 (18.0)	58 (12.2)	36 (15.7)	25 (11.4)	51 (10.8)
Back pain	43 (9.7)	58 (12.2)	22 (9.6)	19 (8.6)	49 (10.3)
Pain in extremity	36 (8.1)	40 (8.4)	14 (6.1)	28 (12.7)	40 (8.4)
Headache	59 (13.3)	75 (15.8)	40 (17.4)	42 (19.1)	94 (19.8)
Breast tenderness [§]	15 (3.4)	13 (2.7)	4 (1.7)	24 (10.9)	14 (3.0)
Vaginal hemorrhage [§]	11 (2.5)	5 (1.1)	8 (3.5)	26 (11.8)	14 (3.0)
Selected cardiac disorders [¶]	1 (0.2)	1 (0.2)	0	0	2 (0.4)
Angina pectoris	0	1 (0.2)	0	0	0
Arteriosclerosis	0	0	0	0	1 (0.2)
Coronary artery disease	1 (0.2)	0	0	0	0
Myocardial infarction	1 (0.2)	0	0	0	1 (0.2)
Selected cerebrovascular AEs [#]	0	1 (0.2)	0	0	0
VTE	0	0	0	1 (0.5)	0
Breast cancer	2 (0.4)**	0	0	1 (0.5) ^{††}	1 (0.2) ^{‡‡}
Breast-related AEs ^{§§}	11 (2.5)	3 (0.6)	4 (1.7)	6 (2.7)	8 (1.7)
Simple ovarian cyst	3 (0.7)	5 (1.1)	2 (0.9)	3 (1.4)	5 (1.1)

SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; BZA, bazedoxifene; MPA, medroxyprogesterone acetate; AE, adverse event; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

*There were no individual AEs that led to discontinuation in >5% of subjects in any treatment group.

[†]Overall $P < 0.05$.

[‡]Overall $P < 0.01$.

[§]Overall $P < 0.001$.

[|]Reported by $\geq 10\%$ of subjects in any group.

[¶]A subject could report ≥ 1 AE within the category of cardiac disorders.

[#]Cerebrovascular accident was the only cerebrovascular-related AE reported.

^{**}Right breast invasive mammary carcinoma for 1 subject, and Stage IIA Nottingham grade I invasive ductal carcinoma for the other.

^{††}Ductal carcinoma in situ and invasive ductal carcinoma grade II.

^{‡‡}Invasive malignant epithelial neoplasm.

^{§§}Includes breast calcifications; breast cyst; breast disorder; breast mass; benign, malignant, or unspecified neoplasms; and abnormal mammograms.

Other Outcome Measures

Effects on Sleep [86]

At 12 months, CE 0.45 mg/BZA 20 mg showed significant improvements in sleep parameters compared with placebo, including time to fall asleep and sleep disturbance ($P < 0.05$). Effects of BZA 20 mg were similar to placebo for all MOS sleep scale parameters. Significant improvements in time to fall asleep, sleep disturbance, sleep adequacy, and sleep problem indices I and II were observed with CE/MPA compared with placebo ($P < 0.05$ for all).

Effects on QOL [86]

CE 0.45 mg/BZA 20 mg and CE/MPA significantly improved total MENQOL score compared with placebo at 12 months ($P < 0.001$ for both). Both CE/BZA and CE/MPA also significantly improved vasomotor function score compared with placebo at 3 and 12 months ($P < 0.001$ for all). Total MENQOL score and individual domain scores were similar for BZA 20 mg and placebo at 12 months.

Effects on Breast Density [16]

There were no significant differences with CE 0.45 mg/BZA 20 mg, BZA 20 mg, or placebo in change from baseline in percent dense breast tissue at 12 months as determined by mammography. The CE/MPA group showed a significant increase in percent dense breast tissue compared with placebo ($P < 0.001$). CE 0.45 mg/BZA 20 mg demonstrated noninferiority compared with placebo in change from baseline in mammographic breast density at 12 months.

Generalizability of Population Treated and Study Limitations (As Stated by Authors)

The **SMART-5** enrolled generally healthy, primarily white women 3 to 4 years postmenopause who were seeking treatment for menopausal symptoms and thus may not be generalizable to less symptomatic postmenopausal women, women of different ethnic origins, or older postmenopausal women who are further from menopause [86]. Other limitations include the 1-year duration of the study which may have limited BMD responses and collection of fracture data [86] and the fact that the BMI requirement prevented enrollment of women who were underweight or obese [86].

Publication Citation/Reference Used Including Funding Source of the Study

Pinkerton JV, Harvey JA, Pan K, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. *Obstet Gynecol.* 2013;121(5):959-968. Funding: supported by Wyeth Research, Collegeville, PA (now Pfizer).

Prospective Effectiveness and Comparative Effectiveness Trials

Prospective effectiveness and comparative effectiveness trials were performed as part of the clinical development program. Please refer to **SMART-1**, **SMART-4**, and **SMART-5** in Section 3.1.1.

Open-Label Safety Extension Studies

There are no open-label safety extension studies to present in this section.

Prospective Studies Examining Other Noneconomic Endpoints

There are currently no prospective studies examining other noneconomic endpoints to present in this section.

Unpublished Data

There are no unpublished data for this section.

3.1.2 All Published and Unpublished Data and Clinical Studies Supporting Off-Label Indications

Although CE 0.45 mg/BZA 20 mg is the only FDA-approved dose, the SMART clinical trial program also focused on CE 0.625 mg/BZA 20 mg; data for this dose are described below. In addition, although not indicated for the treatment of VVA, data for this off-label use of CE/BZA are described below.

SMART-1

Off-Label Use of CE 0.625 mg/BZA 20 mg

The incidence of endometrial hyperplasia was low (<1%) for CE 0.625 mg/BZA 20 mg and not significantly different from placebo over 24 months [4]. CE 0.625 mg/BZA 20 mg significantly increased lumbar spine and total hip BMD from baseline to all time points compared with decreases with placebo ($P < 0.05$) and significantly decreased bone turnover markers compared with placebo at all time points ($P < 0.001$) [5]. CE 0.625 mg/BZA 20 mg significantly reduced the frequency and severity of hot flushes compared with placebo [6]. Rates of cumulative amenorrhea and bleeding/spotting were similar for CE 0.625 mg/BZA 20 mg compared with placebo [7]. Mean percent changes in breast density from baseline to Month 24 were <0.5%, comparable to placebo [8]. CE 0.625 mg/BZA 20 mg was associated with significant improvements in mean quality of sleep ($P < 0.001$), time to fall asleep ($P \leq 0.01$), and minutes slept ($P \leq 0.01$) compared with placebo [9], and significantly improved total MENQOL score and vasomotor function score compared with placebo ($P < 0.001$) [10].

Off-Label Use of CE/BZA for Treatment of VVA

In terms of effects on VVA, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg significantly improved measures of VVA, including significant increases in the mean proportion of intermediate cells and significant decreases in mean proportion of parabasal cells to Month 24 compared with placebo ($P < 0.001$). CE 0.625 mg/BZA 20 mg also significantly increased the mean proportion of superficial cells ($P < 0.01$) compared with placebo [6]. Incidence of dyspareunia was significantly lower with CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg compared with placebo during Weeks 9 to 12 [6].

SMART-2

Off-Label Use of CE 0.625 mg/BZA 20 mg

CE 0.625 mg/BZA 20 mg significantly reduced the mean daily number of moderate and severe hot flushes from baseline compared with placebo for Weeks 2 through 12 ($P < 0.01$). At Week 12, CE 0.625 mg/BZA 20 mg reduced the mean daily number of hot flushes from baseline by 80% compared with 51% for placebo. CE 0.625 mg/BZA 20 mg also significantly reduced the mean daily severity of hot flushes from baseline compared with placebo during Weeks 3 to 12 ($P < 0.001$) [11].

CE 0.625 mg/BZA 20 mg significantly improved MOS sleep scale scores for time to fall asleep, sleep adequacy, sleep disturbance, sleep quantity, and sleep problem indices I and II compared with placebo at Week 12 ($P \leq 0.01$ for all) [12] and showed significantly greater improvements compared with placebo in total MENQOL score and vasomotor, psychosocial, physical, and sexual function domain scores at Week 12 ($P < 0.05$ for all). Results of the MS-TSQ showed that subjects treated with CE 0.625 mg/BZA 20 mg compared with placebo had significantly greater overall satisfaction with treatment and significantly greater satisfaction in ability to control hot flushes during the day and night, effect on quality of sleep, effect on mood or emotions, and satisfaction with tolerability to side effects ($P < 0.05$ for all) [12].

SMART-3

Off-Label Use of CE 0.625 mg/BZA 20 mg

CE 0.625 mg/BZA 20 mg improved sexual function at Week 12 based on individual item scores and the total ASEX score; significant improvement versus placebo was observed in ease of lubrication score ($P < 0.01$) [15]. CE 0.625 mg/BZA 20 mg significantly improved vasomotor function, sexual function, physical function, and total MENQOL scores at Week 12 compared with placebo ($P < 0.05$ for all). Subjects receiving CE 0.625 mg/BZA 20 mg had significantly greater overall satisfaction on the MS-TSQ compared with placebo ($P < 0.001$) and significantly greater satisfaction for control of hot flushes during the day and night, effect on quality of sleep, effect on mood or emotions, and tolerability to side effects ($P < 0.05$ for all) [15].

Off-Label Use of CE/BZA for Treatment of VVA

CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg significantly increased the percentage of superficial cells and intermediate cells and decreased the percentage of parabasal cells compared with placebo ($P < 0.01$) and BZA 20 mg ($P < 0.001$). CE 0.625 mg/BZA 20 mg also significantly improved vaginal pH ($P < 0.001$) and most bothersome VVA symptom compared with placebo ($P < 0.05$). Significant improvements in vaginal dryness were observed with both CE/BZA doses compared with placebo ($P < 0.05$) [14].

SMART-5

Off-Label Use of CE 0.625 mg/BZA 20 mg

Rates of endometrial hyperplasia ($< 1\%$) with CE 0.625 mg/BZA 20 mg were similar to those of other treatment groups. CE 0.625 mg/BZA 20 mg showed significantly greater increases from baseline in endometrial thickness compared with placebo ($P < 0.001$). CE 0.625 mg/BZA 20 mg significantly increased lumbar spine, total hip, and femoral neck BMD and significantly decreased serum bone turnover markers compared with placebo at 12 months ($P < 0.01$ for all) [86].

Rates of cumulative amenorrhea were high with CE 0.625 mg/BZA 20 mg and similar to placebo over 1 year of treatment and significantly higher than those for CE/MPA at all time points ($P < 0.001$) [86]. Incidence of breast tenderness was similar for CE 0.625 mg/BZA 20 mg and placebo, but significantly lower than for CE/MPA ($P < 0.01$) [16].

At 12 months, CE 0.625 mg/BZA 20 mg significantly improved time to fall asleep, sleep disturbance, sleep adequacy, and sleep problem indices I and II compared with placebo ($P < 0.05$ for all) [86]. At 12 months, CE 0.625 mg/BZA 20 mg significantly improved total MENQOL score as well as vasomotor, physical, and sexual function domain scores compared with placebo ($P < 0.01$ for all) [86]. Change from baseline in percent dense breast tissue at 12 months was similar for CE 0.625 mg/BZA 20 mg and placebo

[16]. CE 0.625 mg/BZA 20 mg demonstrated noninferiority compared with placebo in change from baseline in mammographic breast density at 12 months.

Ongoing Pfizer-Sponsored Clinical Development Studies

Please refer to section 2.1.6 for a complete list of ongoing clinical development studies. Additionally, information for Pfizer clinical trials can be found at www.clinicaltrials.gov.

3.1.3 Clinical Evidence Spreadsheets of All Published and Unpublished Trials

Table 3.13. Evidence Table of Clinical Studies for CE/BZA

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results						
SMART-1 [4-10] Phase 3 US, Europe, and Brazil	2-year, outpatient, randomized, double-blind, PBO- and active-controlled, phase 3 study	Healthy, postmenopausal women aged 40-75 years with an intact uterus and acceptable endometrial biopsy results at screening (N = 3,397)	CE 0.625 mg/BZA 10 mg (n = 430)	Primary efficacy endpoint: Incidence of endometrial hyperplasia at Month 12 (main study); lumbar spine BMD at Month 24 (Osteoporosis Prevention I and II Substudies)	Endometrial safety <i>Incidence of Endometrial Hyperplasia at Month 12 (Primary Endpoint)*</i>						
			CE 0.625 mg/BZA 20 mg (n = 414)								
		Osteoporosis Prevention Substudies I (n = 1,454) and II (n = 861)	CE 0.625 mg/BZA 40 mg (n = 417)	Secondary efficacy endpoints: • Endometrial hyperplasia at Months 6 & 24 • Hip and lumbar spine BMD at Months 6, 12, 18, & 24 • Effects on VMS • Amenorrhea/bleeding profile • Breast pain	<table border="1"> <thead> <tr> <th colspan="2">CE 0.45 mg/BZA 20 mg</th> </tr> </thead> <tbody> <tr> <td>Total cases (%)</td> <td>0 (0.00)</td> </tr> <tr> <td>95% CI (%)</td> <td>0.00-1.09</td> </tr> </tbody> </table> <p>*No hyperplasia was observed with PBO at Month 12.</p> <ul style="list-style-type: none"> • At Month 24, endometrial hyperplasia rates were similar for CE 0.45 mg/BZA 20 mg and PBO (difference ± SE, 0.34 ± 0.34) • No significant difference in increase from baseline in endometrial thickness for CE 0.45 mg/BZA 20 mg vs PBO at Month 12 or 24 	CE 0.45 mg/BZA 20 mg		Total cases (%)	0 (0.00)	95% CI (%)	0.00-1.09
CE 0.45 mg/BZA 20 mg											
Total cases (%)	0 (0.00)										
95% CI (%)	0.00-1.09										
		Retrospective ancillary breast substudy (n = 507)	CE 0.45 mg/BZA 10 mg (n = 430)	Safety	Effects on bone • In the Osteoporosis Prevention I and II Substudies, CE 0.45 mg/BZA 20 mg significantly increased lumbar spine and total hip BMD from baseline to all time points vs decreases with PBO (<i>P</i> <0.05) • Bone turnover markers significantly decreased with CE 0.45 mg/BZA 20 mg vs PBO at all time points (<i>P</i> <0.001)						
			CE 0.45 mg/BZA 20 mg (n = 433)			Other outcome measures: • Breast density (ancillary substudy) • Sleep parameters • QOL (MENQOL)	Effects on VMS CE 0.45 mg/BZA 20 mg significantly reduced the frequency (<i>P</i> <0.05) and severity (<i>P</i> <0.001) of hot flushes vs PBO				
			CE 0.45 mg/BZA 40 mg (n = 423)	Vaginal bleeding/amenorrhea Rates of cumulative amenorrhea and bleeding/spotting were similar for CE 0.45 mg/BZA 20 mg vs PBO	Safety • Incidences of AEs, including VTEs and cardiovascular AEs, and breast pain were similar between CE/BZA and PBO • Majority of TEAEs were mild to moderate in severity and not considered related to study drug						
			RLX 60 mg (n = 423)			Other outcome measures • Mean percent changes in breast density from baseline to Month 24 were small (<0.5%) and comparable for CE 0.45 mg/BZA 20 mg and PBO • CE 0.45 mg/BZA 20 mg was associated with significant improvements in mean quality of sleep (<i>P</i> ≤0.01), time to fall asleep (<i>P</i> ≤0.01), and minutes slept (<i>P</i> <0.05) vs PBO • CE 0.45 mg/BZA 20 mg significantly improved total MENQOL score and vasomotor function score vs PBO (<i>P</i> <0.001)					
			PBO (n = 427)								

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results																								
SMART-2 [11-13] Phase 3 US	12-week, outpatient, randomized, double-blind, PBO-controlled, phase 3 study	Healthy, postmenopausal women aged 40-65 years with an intact uterus and ≥ 7 moderate to severe hot flushes per day (or ≥ 50 per week) at screening (N = 318)	CE 0.45 mg/BZA 20 mg (n = 127) CE 0.625 mg/BZA 20 mg (n = 128) PBO (n = 63)	<p>Primary efficacy endpoint: Change from baseline in mean daily number and severity of hot flushes at Weeks 4 and 12</p> <p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> Percentage of responders ($\geq 50\%$ or $\geq 75\%$ reduction in number of hot flushes) Breast pain Sleep parameters (MOS sleep scale) QOL (MENQOL) <p>Safety</p> <p>Other outcome measures: Satisfaction with treatment (MS-TSQ)</p>	<p>Effects on VMS CE 0.45 mg/BZA 20 mg significantly reduced the mean daily number and severity of hot flushes from baseline vs PBO during Weeks 3-12 ($P < 0.01$)</p> <table border="1"> <thead> <tr> <th>Daily number of moderate and severe hot flushes</th> <th>CE 0.45 mg/BZA 20 mg</th> <th>PBO</th> </tr> </thead> <tbody> <tr> <td>Mean</td> <td></td> <td></td> </tr> <tr> <td>Baseline</td> <td>10.3</td> <td>10.5</td> </tr> <tr> <td>Week 12</td> <td>2.8^a</td> <td>5.4</td> </tr> <tr> <td>Percent reduction</td> <td>74%</td> <td>51%</td> </tr> <tr> <td>Responder rates at Week 12</td> <td></td> <td></td> </tr> <tr> <td>$\geq 75\%$ decrease</td> <td>61%^a</td> <td>27%</td> </tr> <tr> <td>$\geq 50\%$ decrease</td> <td>83%^a</td> <td>52%</td> </tr> </tbody> </table> <p>^a$P < 0.001$ vs PBO.</p> <p>Effects on sleep CE 0.45 mg/BZA 20 mg significantly improved MOS sleep scale scores for time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II vs PBO at Week 12 ($P < 0.001$)</p> <p>Effects on QOL CE 0.45 mg/BZA 20 mg showed significantly greater improvements vs PBO in vasomotor function and total MENQOL score at Week 12 ($P < 0.001$)</p> <p>Safety</p> <ul style="list-style-type: none"> Overall, no significant differences among CE/BZA and PBO groups in number of participants reporting any TEAE, including those reporting ≥ 1 day of breast pain, or incidence of AEs resulting in study discontinuation No VTEs, superficial venous thrombosis, or cerebrovascular events reported <p>Other outcome measures</p> <ul style="list-style-type: none"> Results of the MS-TSQ showed significantly greater overall satisfaction with treatment ($P < 0.001$), and significantly greater satisfaction in ability to control hot flushes during the day ($P < 0.001$) and night ($P < 0.001$), effect on quality of sleep ($P < 0.001$), effect on mood or emotions ($P < 0.05$), effect on ability to concentrate ($P < 0.05$), and satisfaction with tolerability to side effects ($P < 0.01$) with CE 0.45 mg/BZA 20 mg vs PBO In a secondary analysis, CE 0.45 mg/BZA 20 mg significantly increased the number of hot flush symptom-free days from Weeks 3-12 ($P < 0.05$) and the proportion of women without moderate or severe hot flushes at Week 12 ($P < 0.01$) vs PBO 	Daily number of moderate and severe hot flushes	CE 0.45 mg/BZA 20 mg	PBO	Mean			Baseline	10.3	10.5	Week 12	2.8 ^a	5.4	Percent reduction	74%	51%	Responder rates at Week 12			$\geq 75\%$ decrease	61% ^a	27%	$\geq 50\%$ decrease	83% ^a	52%
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SMART-3 [14,15]	12-week, randomized, double-blind, PBO-controlled, comparator phase 3 study	Healthy, postmenopausal women aged 40-65 years with an intact uterus, vaginal cytological smear showing vaginal pH >5.0 and ≤5% superficial cells, and ≥1 bothersome moderate to severe symptom of VVA at screening (N = 652)	CE 0.45 mg/BZA 20 mg (n = 219) CE 0.625 mg/BZA 20 mg (n = 218) BZA 20 mg (n = 110) PBO (n = 105)	Primary efficacy endpoints: Severity of most bothersome VVA symptom, vaginal pH, proportion of vaginal superficial cells, and proportion of vaginal parabasal cells Secondary efficacy endpoints: Individual VVA symptoms (eg, vaginal dryness, itching, dyspareunia) Safety Other outcome measures: <ul style="list-style-type: none"> Sexual function (ASEX) QOL (MENQOL) Satisfaction with treatment (MS-TSQ) 	Efficacy/effects on VVA CE/BZA is not indicated for the treatment of VVA and, thus, results for these efficacy endpoints will not be presented in this section Safety <ul style="list-style-type: none"> Incidence of TEAEs and discontinuations due to AEs was similar across treatment groups Most TEAEs were mild to moderate in severity Incidence of gynecologic TEAEs, including breast pain, ovarian cysts, and vaginal bleeding, was not significantly different with CE/BZA vs PBO Other outcome measures <table border="1"> <thead> <tr> <th>Mean change from baseline to Week 12</th> <th>CE 0.45 mg/ BZA 20 mg</th> <th>PBO</th> </tr> </thead> <tbody> <tr><td>Total ASEX score</td><td>-1.87</td><td>-1.34</td></tr> <tr><td>Sex drive</td><td>-0.29</td><td>-0.18</td></tr> <tr><td>Ease of arousal</td><td>-0.30</td><td>-0.20</td></tr> <tr><td>Ease of lubrication</td><td>-0.82[†]</td><td>-0.50</td></tr> <tr><td>Ease of orgasm</td><td>-0.28</td><td>-0.39</td></tr> <tr><td>Satisfaction with orgasm</td><td>-0.19</td><td>-0.23</td></tr> <tr><td>Total MENQOL score</td><td>-1.09[†]</td><td>-0.67</td></tr> <tr><td>Vasomotor function</td><td>-1.33[†]</td><td>-0.51</td></tr> <tr><td>Sexual function</td><td>-1.95[†]</td><td>-1.24</td></tr> <tr><td>Physical function</td><td>-0.64</td><td>-0.42</td></tr> <tr><td>Psychosocial function</td><td>-0.45</td><td>-0.49</td></tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Subjects with satisfaction at Week 12</th> <th>CE 0.45 mg/ BZA 20 mg</th> <th>PBO</th> </tr> </thead> <tbody> <tr><td>Overall satisfaction on MS-TSQ</td><td>62.6%[‡]</td><td>47.4%</td></tr> <tr><td>Ability to control hot flushes during the day</td><td>58.9%[‡]</td><td>35.1%</td></tr> <tr><td>Ability to control hot flushes during the night</td><td>55.9%[‡]</td><td>38.3%</td></tr> <tr><td>Effect on ability to concentrate</td><td>40.4%</td><td>41.1%</td></tr> <tr><td>Effect on interest in sex</td><td>38.6%</td><td>31.6%</td></tr> <tr><td>Effect on mood or emotions</td><td>56.7%[‡]</td><td>33.0%</td></tr> <tr><td>Effect on quality of sleep</td><td>50.3%[‡]</td><td>27.7%</td></tr> <tr><td>Tolerability to side effects</td><td>76.9%</td><td>63.2%</td></tr> </tbody> </table>	Mean change from baseline to Week 12	CE 0.45 mg/ BZA 20 mg	PBO	Total ASEX score	-1.87	-1.34	Sex drive	-0.29	-0.18	Ease of arousal	-0.30	-0.20	Ease of lubrication	-0.82 [†]	-0.50	Ease of orgasm	-0.28	-0.39	Satisfaction with orgasm	-0.19	-0.23	Total MENQOL score	-1.09 [†]	-0.67	Vasomotor function	-1.33 [†]	-0.51	Sexual function	-1.95 [†]	-1.24	Physical function	-0.64	-0.42	Psychosocial function	-0.45	-0.49	Subjects with satisfaction at Week 12	CE 0.45 mg/ BZA 20 mg	PBO	Overall satisfaction on MS-TSQ	62.6% [‡]	47.4%	Ability to control hot flushes during the day	58.9% [‡]	35.1%	Ability to control hot flushes during the night	55.9% [‡]	38.3%	Effect on ability to concentrate	40.4%	41.1%	Effect on interest in sex	38.6%	31.6%	Effect on mood or emotions	56.7% [‡]	33.0%	Effect on quality of sleep	50.3% [‡]	27.7%	Tolerability to side effects	76.9%	63.2%
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^{*}P <0.05 vs PBO.
[†]P ≤0.001 vs PBO.
[‡]P <0.001 vs PBO.

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results															
SMART-4 [3] Phase 3 US and Argentina	1-year, multicenter, double-blind, PBO- and active-controlled, phase 3 study	Healthy, postmenopausal women aged 40- <65 years with an intact uterus and an acceptable endometrial biopsy report at screening (N = 1,061)	CE 0.45 mg/BZA 20 mg (n = 361) CE 0.625 mg/BZA 20 mg (n = 349) CE 0.45 mg/MPA 1.5 mg (n = 179) PBO (n = 172)	Primary efficacy endpoint: Incidence of endometrial hyperplasia at 1 year (main study); percent change in lumbar spine BMD at 1 year (osteoporosis substudy) Secondary efficacy endpoints: <ul style="list-style-type: none"> Cumulative and noncumulative amenorrhea rates Breast pain Change from baseline in hip BMD and bone metabolism profile (osteoporosis substudy) Safety	Efficacy and endometrial safety results with CE/BZA will not be presented because reduced bioavailability of BZA in the formulation used in this trial led to insufficient endometrial protection with CE/BZA Safety <ul style="list-style-type: none"> No significant differences among groups in overall incidences of AEs, TEAEs, serious AEs, and study discontinuations due to AEs Significantly lower rates of study discontinuations due to bleeding-related AEs with CE/BZA vs CE/MPA ($P < 0.01$ for all) Incidences of AEs of special interest, including selected cardiac events, cerebrovascular events, and reproductive tract and breast-related AEs were similar among groups 															
SMART-5 [16] [86] Phase 3 Global	1-year, multicenter, international, randomized, double-blind, PBO- and active-controlled, phase 3 study	Healthy, postmenopausal women aged 40-65 years with an intact uterus, an acceptable endometrial biopsy report at screening, and were seeking treatment for menopausal symptoms (N = 1,843) Osteoporosis substudy (n = 590) Breast density substudy (n = 940)	CE 0.45 mg/BZA 20 mg (n = 445) CE 0.625 mg/BZA 20 mg (n = 474) BZA 20 mg (n = 230) CE 0.45 mg/MPA 1.5 mg (n = 220) PBO (n = 474)	Primary efficacy endpoint: Incidence of endometrial hyperplasia at 12 months (main study); percent change from baseline in lumbar spine BMD at 12 months (osteoporosis substudy) Secondary efficacy endpoints: <ul style="list-style-type: none"> Cumulative amenorrhea rate Breast tenderness Change from baseline in total hip BMD and bone turnover markers (osteoporosis substudy) Safety Other outcome measures: <ul style="list-style-type: none"> Sleep (MOS sleep scale; sleep/QOL substudy) QOL (MENQOL; sleep/QOL substudy) Change from baseline in breast density (breast density substudy) 	Primary Efficacy Endpoints at Month 12 <table border="1"> <thead> <tr> <th></th> <th>CE/BZA</th> <th>BZA</th> <th>CE/MPA</th> <th>PBO</th> </tr> </thead> <tbody> <tr> <td>Endometrial hyperplasia, n/N (%)</td> <td>1/335 (0.30)</td> <td>0/169</td> <td>0/149</td> <td>1/354 (0.28)</td> </tr> <tr> <td>Mean (SE) percent change in lumbar spine BMD</td> <td>0.24 (0.29)*</td> <td>0.07 (0.40)*</td> <td>1.30 (0.39)*</td> <td>-1.28 (0.28)</td> </tr> </tbody> </table> CE 0.45 mg/BZA 20 mg; BZA 20 mg; CE 0.45 mg/MPA 1.5 mg. * $P < 0.01$ vs PBO. Endometrial safety <ul style="list-style-type: none"> Rates of endometrial hyperplasia were <1% and similar for all groups CE 0.45 mg/BZA 20 mg ($P < 0.05$) and CE 0.45 mg/MPA 1.5 mg ($P < 0.001$) showed significantly greater increases from baseline in endometrial thickness vs PBO Incidence of proliferative endometrium was <1% and similar among groups Effects on bone <ul style="list-style-type: none"> CE 0.45 mg/BZA 20 mg, BZA 20 mg, and CE 0.45 mg/MPA 1.5 mg significantly increased lumbar spine, total hip, and femoral neck BMD vs PBO at 12 months ($P < 0.01$ for all) CE 0.45 mg/BZA 20 mg, BZA 20 mg, and CE/MPA showed significantly greater decreases from baseline in serum bone turnover markers vs PBO at 12 months ($P < 0.01$ for all) No differences among groups in incidence of fractures reported as 		CE/BZA	BZA	CE/MPA	PBO	Endometrial hyperplasia, n/N (%)	1/335 (0.30)	0/169	0/149	1/354 (0.28)	Mean (SE) percent change in lumbar spine BMD	0.24 (0.29)*	0.07 (0.40)*	1.30 (0.39)*	-1.28 (0.28)
	CE/BZA	BZA	CE/MPA	PBO																
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Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
					<p>AEs, although study was not specifically powered for fracture detection</p> <p>Vaginal bleeding/amenorrhea Cumulative amenorrhea rates were similar for CE 0.45 mg/BZA 20 mg, BZA 20 mg, and PBO over 1 year and significantly higher vs CE/MPA at all time points ($P < 0.001$)</p> <p>Breast tenderness Percentage of subjects with ≥ 1 day of breast tenderness was similar for CE 0.45 mg/BZA 20 mg, BZA alone, and PBO but significantly lower than with CE/MPA ($P < 0.001$ vs PBO and $P < 0.01$ vs CE/BZA or BZA alone for all time periods)</p> <p>Safety</p> <ul style="list-style-type: none"> • Incidences of AEs, TEAEs, and serious AEs were similar with CE/BZA and PBO • More subjects in the CE/MPA group discontinued due to AEs vs other groups • No differences among groups in rates of selected cardiac, cerebrovascular, or breast-related AEs • Incidence of bleeding-related AEs was similar with CE/BZA and PBO and significantly lower vs CE/MPA (overall $P < 0.001$) <p>Other outcome measures</p> <ul style="list-style-type: none"> • At 12 months, CE 0.45 mg/BZA 20 mg significantly improved sleep parameters vs PBO, including time to fall asleep and sleep disturbance ($P < 0.05$); CE/MPA significantly improved time to fall asleep, sleep disturbance, sleep adequacy, and sleep problem indices I and II vs PBO ($P < 0.05$ for all) • CE 0.45 mg/BZA 20 mg and CE/MPA significantly improved total MENQOL score vs PBO at 12 months and vasomotor function score at 3 and 12 months ($P < 0.001$ for all) • Effects of BZA 20 mg on sleep and QOL were similar to PBO • No significant differences with CE 0.45 mg/BZA 20 mg, BZA 20 mg, or PBO in change from baseline in percent dense breast tissue at 12 months; CE/MPA showed significant increase in percent dense breast tissue vs PBO ($P < 0.001$); CE/BZA demonstrated noninferiority vs PBO in change from baseline in mammographic breast density at 12 months

CE, conjugated estrogens; BZA, bazedoxifene; SMART, Selective estrogen, Menopause, And Response to Therapy; PBO, placebo; BMD, bone mineral density; RLX, raloxifene; VMS, vasomotor symptoms; QOL, quality of life; MENQOL, Menopause-Specific Quality of Life; CI, confidence interval; SE, standard error; AE, adverse event; VTE, venous thromboembolism; TEAE, treatment-emergent adverse event; MOS, Medical Outcomes Study; MS-TSQ, Menopause Symptoms-Treatment Satisfaction Questionnaire; VVA, vulvar/vaginal atrophy; ASEX, Arizona Sexual Experiences Scale; MPA, medroxyprogesterone acetate.

3.1.4 Summary of Evidence From Secondary Sources

Pfizer is not aware of any evidence from secondary sources to present in this section at this time.

4.0 ECONOMIC VALUE: BURDEN OF ABNORMAL UTERINE BLEEDING EVALUATION IN WOMEN TREATED WITH CONJUGATED ESTROGENS COMBINED WITH MEDROXYPROGESTERONE ACETATE OR BAZEDOXIFENE

4.1 Introduction/Background

4.1.1 Introduction

Postmenopausal women treated with estrogen-progestogen therapy (EPT) for vasomotor symptoms commonly present to healthcare providers with complaints of sustained, abnormal vaginal bleeding, with 41% of women starting continuous-combined HRT presenting to their physician for postmenopausal bleeding (PMB) [92]. PMB is most common in the early months after initiating EPT, and tends to decrease over time [93]. For some women such bleeding may be an adverse effect of hormone replacement therapy, while for others it may indicate more serious underlying pathology [93]. Patients presenting to a healthcare provider with PMB should be evaluated to distinguish benign PMB from PMB due to underlying pathology [94]. The evaluation of abnormal bleeding may include non-invasive and invasive procedures, including endometrial biopsy and transvaginal ultrasound (TVU) [94].

The present analysis was conducted to estimate the annual volume of procedures performed in the United States (US) for abnormal PMB evaluation in non-hysterectomized postmenopausal women (aged 40-64) receiving conjugated estrogens plus medroxyprogesterone acetate (CE/MPA) for moderate to very severe VMS. The model then estimates the reduction in such procedures that would occur if these women were alternatively treated with CE/BZA.

4.1.2 Objective

This model was developed in order to:

- Estimate the total number of clinical procedures in the US population which result from evaluation of uterine bleeding during therapy with CE/BZA and with CE/MPA.
- Estimate the total number of procedures that could be potentially averted with the use of CE/BZA instead of CE/MPA.

4.2 Methods

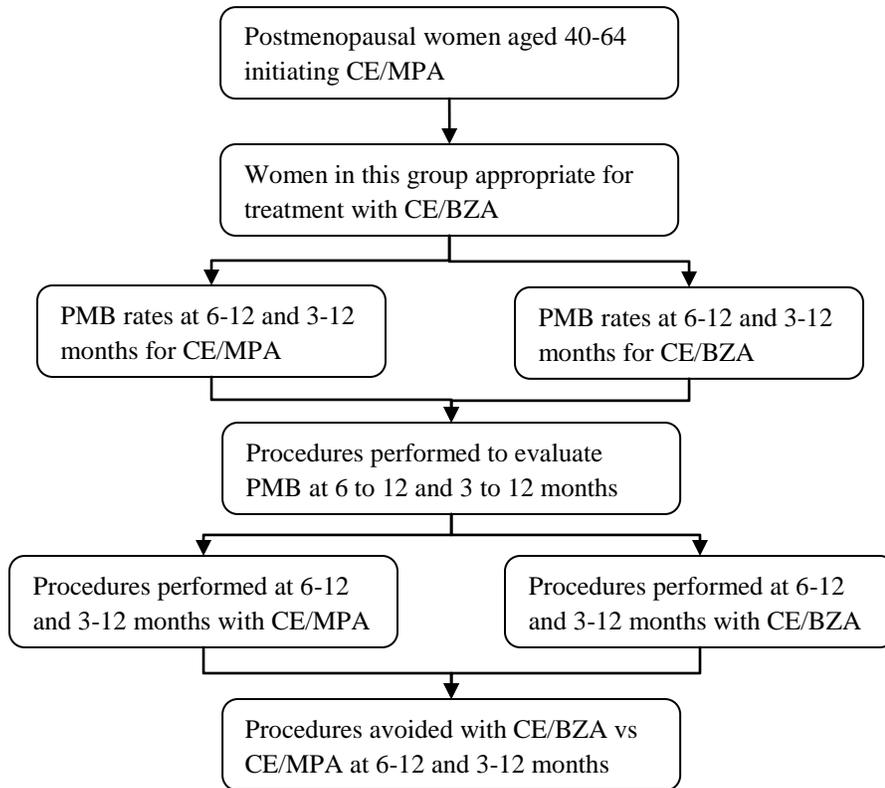
A simulation model was developed to estimate the outcomes listed in Section 4.1.2 in patients presenting with PMB 6 to 12 months (base case) or 3 to 12 months (scenario analysis) after therapy initiation. The model is divided into 2 sections; potential patient population and evaluative procedures algorithm.

The potential patient population was calculated using the number of women who are treated with CE/MPA, derived from market research data [95], combined with the percentage of treated women who develop PMB 6 to 12 and 3 to 12 months after therapy initiation for both CE/MPA and CE/BZA, estimated using prospective randomized trial data.

This cohort of women entered a PMB clinical evaluation algorithm, estimated from published guidelines [96] and a survey of 5 expert HCP’s with ongoing, real-world experience treating patients for postmenopausal bleeding.

The number of evaluative procedures in the CE/BZA arm was estimated by replacing CE/MPA bleeding rates with CE/BZA bleeding rates in the evaluation algorithm, as it was assumed that the potential market share of CE/BZA is approximately equal to that of CE/MPA.

Figure 4.1. Model structure



4.2.1 Model Inputs

There are 2 basic components to the model; patient population and PMB evaluative procedures. The key inputs are described below.

Calculation of patient population

Women treated with CE/MPA

The number of women treated with CE/BZA who would also be appropriate for treatment with CE/BZA was derived from IMS Market Share data [95].

The relevant patient sample extracted from the IMS market share data was defined by the following characteristics. The number of women who are contraindicated for CE/MPA was calculated from diagnoses-stratified market share data where diagnoses were defined by International Classification of Diseases (ICD-9) coding [97].

- Women aged 40-64
- Treated with low dose CE/MPA
- New patients within a 1 year time frame (from July 2012 to June 2013)
- Non-contraindicated for treatment with CE/BZA

Table 4.1. Women treated with CE/MPA

Name	N
New patients*	124,594
Contraindicated for CE/BZA	
With hypothyroidism (unspecified) †	6027
With postmenopausal vaginal atrophy with or without uterine leiomyoma †	20,253
With dyspareunia †	3923
With postmenopausal bleeding †	9640
Total contraindicated for CE/BZA	39,843
Total patients (from Oct 2011 to Sep 2013)	535,852

*New patients from July 2012 to June 2013

† Among all patients October 2011 to September 2013.

The percent of patients on CE/BZA who are contraindicated for CE/BZA is 7.4% (39,843/535,852). The total number of new patients on CE/MPA who are appropriate for CE/BZA is 115,330 (i.e., 124,594 – [124,594 x 0.074]).

Uterine bleeding rates

The number of treated women who develop PMB 6 to 12 and 3 to 12 months after therapy initiation was subsequently estimated by pooling the inverse of cumulative amenorrhea rates reported in 4 phase 3 clinical trials; SMART-1, SMART-4, SMART-5 and HOPE. The data represents the percentage of women recording in daily vaginal bleeding diaries any day of PMB 6 to 12 or 3 to 12 months after therapy initiation. Table 4.2 describes key trial characteristics by treatment group. Table 4.3 presents the resulting pooled bleeding rates.

Table 4.2. Phase 3 clinical trials used in creating pooled uterine bleeding rates

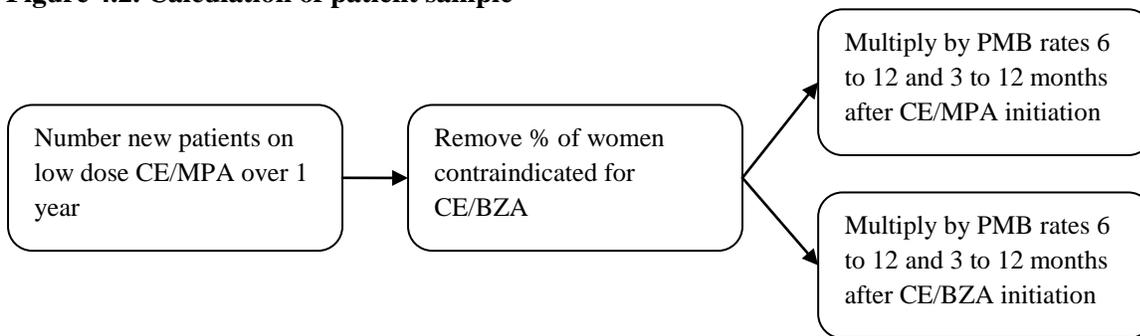
CE/MPA (0.45/1.5 mg)			
Trials Used	SMART-5 [98]	SMART-4 [3]	HOPE [99]
Design	double-blind; randomized; placebo- and active-controlled	double-blind; randomized; placebo- and active- (CE/MPA) controlled	double-blind; double-dummy; placebo/active-drug-controlled
Population	postmenopausal women; ages 40-64 years; with an intact uterus	postmenopausal women; ages 40-64 years; with an intact uterus	postmenopausal women; ages 40-64 years; with an intact uterus
Comparators	CE 0.45, 0.625 mg / BZA 20 mg; BZA 20 mg; CE 0.45 mg / MPA 1.5 mg; placebo	CE 0.425, 0.625 mg / BZA 20 mg; CE 0.45 mg / MPA 1.5 mg; placebo	8 CE/MPA and/or placebo combinations
Primary outcome	Endometrial safety; osteoporosis prevention	Endometrial safety; osteoporosis prevention	Endometrial safety; osteoporosis prevention; vasomotor symptoms
CE/BZA (0.45/20 mg)			
Trials Used	SMART-5 [98]	SMART -1 [6]	
Design	double-blind, randomized, placebo- and active-controlled	double-blind; randomized; placebo- and active- (raloxifene) controlled	
Population	postmenopausal women; ages 40-64 years; with an intact uterus	postmenopausal women; ages 40-75 years; with an intact uterus	
Comparators	CE 0.45, 0.625 mg / BZA 20 mg; BZA 20 mg; CE 0.45 mg / MPA 1.5 mg; placebo	CE 0.425, 0.625 mg / BZA 10, 20, 40 mg; raloxifene 60 mg; placebo	
Primary outcome	Endometrial safety; osteoporosis prevention	Endometrial safety; osteoporosis prevention; vasomotor symptoms	

Table 4.3. Pooled uterine bleeding rates

	%	N (total)	N (with PMB)
Treated with CE/MPA (0.45/1.5 mg)			
Bleeding at 6 to 12 months	39.76	654	260
Bleeding at 3 to 12 months	50.29	684	344
Treated with CE/BZA (0.45/20 mg)			
Bleeding at 6 to 12 months	12.56	788	99
Bleeding at 3 to 12 months	17.65	810	143

PMB rates come from Modified Intent to Treat (MITT) populations for all

Figure 4.2. Calculation of patient sample



PMB evaluation pathway

The PMB evaluation pathway was applied to the patient population identified above (Figure 4.2). In this pathway, PMB is evaluated by procedures (and/or combinations of procedures) that include:

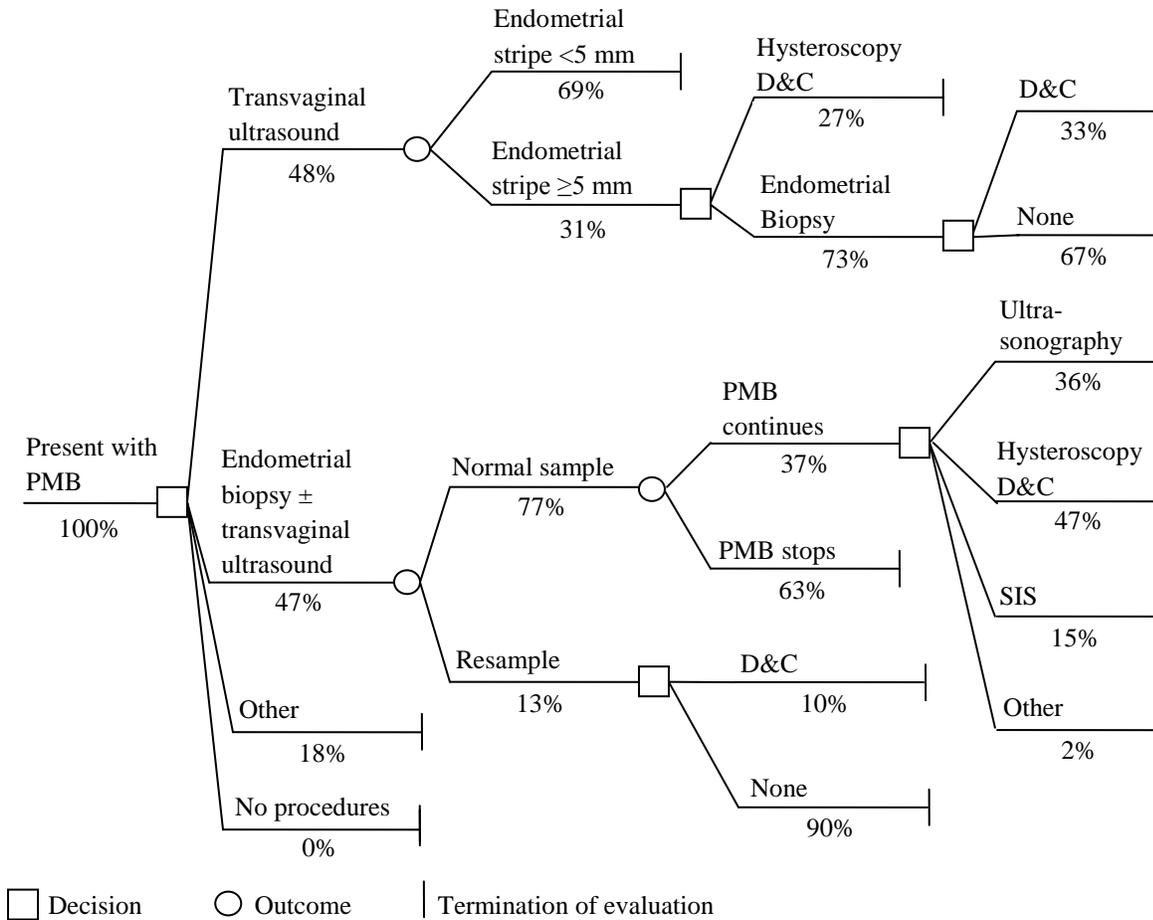
- Transvaginal ultrasound (TVU)
- Endometrial biopsy ± transvaginal ultrasound
- Dilation and curettage (D&C)
- Hysteroscopy D&C
- Ultrasonography
- Saline infusion sonohysterography (SIS)

The model is organized such that patients (treated with either CE/MPA or CE/BZA presenting with PMB after 6 to 12 or 3 to 12 months of initiating hormonal therapy) transit through the PMB evaluation pathway until either pathology is defined (i.e., PMB is not an adverse event of hormonal therapy) or until they reach the bottom row (after which no additional evaluations are performed). PMB evaluation procedures are accumulated accordingly. Hormonal therapies (CE/MPA vs. CE/BZA) are compared at both time-points (6 to 12 and 3 to 12 months) on the basis of procedure volume.

The proportions of patients transitioning through the model nodes were elicited from a survey of 5 expert healthcare providers (HCP) with ongoing, real-world experience treating patients under these circumstances. Their responses are incorporated into the model such that the user can choose the HCP and the model will automatically repopulate with the respective HCP-estimates. The base-model shows the mean of responses across the 5 expert HCP’s.

To calculate the number of procedures within a specific node of the PMB evaluation pathway per HCP, the percentage in the relevant cell is multiplied by the number of patients entering the node.

Figure 4.3. Evaluative procedures algorithm and mean healthcare provider survey responses



Mean responses provided below each node

Among the healthcare providers surveyed, procedures reflected by this model did not change based on a patient presenting with PMB 6 to 12 or 3 to 12 months.

Table 4.4. Healthcare provider details

HCP	Practice location (state)	Specialty	Number of female patients seen per month	Number of postmenopausal, non-hysterectomized patients seen per month
1	IN	MD, OB/Gyn	250	35
2	MD	MD, OB/Gyn	250	200
3	TN	Women’s Health Nurse Practitioner, Board Certified	250	60
4	CA	MD, OB/Gyn	Not available	Not available
5	CT	MD, Reproductive Endocrinology	150	Not available

4.3 Model Results

Based on the model and its assumptions, approximately 115,330 of the 124,594 women initiating CE/MPA therapy from (time frame) were appropriate for treatment with CE/BZA. Among these women, 40% may experience PMB 6 to 12 months and 50% may experience PMB 3 to 12 months after therapy initiation.

The average procedure volumes in the CE/MPA arm were 63,245 (6 to 12 months) and 79,995 (3 to 12 months). If these patients were alternatively initiated with CE/BZA, the model predicted an annual reduction of 44,752 procedures (71%) for PMB occurring 6 to 12 months after therapy initiation and of 54,007 (68%) for PMB occurring 3 to 12 months after therapy initiation.

A probabilistic sensitivity analysis was conducted where PMB and mean values from the evaluative procedures survey results were simultaneously varied based on beta distributions to generate 1000 unique model replicates for each of the 2 time-horizons. From this analysis, the median number of evaluation procedures avoided through the use of CE/BZA over CE/MPA was 44,761 among women with PMB 6 to 12 months and 54,043 among women with PMB 3 to 12 months after therapy initiation.

Table 4.5. Results in patients presenting with PMB 6 to 12 months after initiating treatment

Procedure	Total number of procedures		
	CE/MPA	CE/BZA	Difference
Total	63,245	18,493	44,752
D&C alone	2311	676	1635
With hysteroscopy	5108	1494	3614
Endometrial biopsy alone	8353	2443	5911
With TVU	20,311	5939	14,372
SIS alone	995	291	704
TVU alone	23,779	6953	16,826
Ultrasound alone	2388	698	1690
PSA results			44,761

Table 4.6. Results in patients presenting with PMB 3 to 12 months after initiating treatment

Procedure	Total number of procedures		
	CE/MPA	CE/BZA	Difference
Total	79,995	25,988	54,007
D&C alone	2923	950	1974
With hysteroscopy	6461	2099	4362
Endometrial biopsy alone	10,566	3432	7133
With TVU	25,690	8346	17,344
SIS alone	1259	409	850
TVU alone	30,076	9771	20,305
Ultrasound alone	3020	981	2039
PSA results			54,043

4.4 Limitations

- 3 to 12 months after therapy initiation may not be relevant because many HCPs may not evaluate at that time. However, 3 of 5 clinician survey respondents indicated that workup would be the same at 3 months from EPT initiation as at 6 months.
- Due to restricted availability of studies reporting the process of evaluating PMB patients matching the cohort used in this study, the sequence of PMB-evaluative procedures as reported by the five HCP's surveyed in this study may not be fully representative of PMB-evaluative care in the United States after EPT initiation.
- Survey was conducted with postmenopausal, non-hysterectomized patients aged 40-64 in mind. The effect of "post-menopausal" is unclear. It likely affects individual cohort totals but not the proportional difference between treatment groups.
- Women aged 64 at indexing could have aged out by the follow-up times. This might be balanced by women aged 39 who could have aged-in by the follow-up times. Whether this causes over- or under-estimation would be due to population factors at the time.
- The findings in this study cannot be used to demonstrate a causal relationship between CE/BZA or CE/MPA and postmenopausal bleeding or between CE/BZA or CE/MPA and consequences of postmenopausal bleeding (e.g, work-up after postmenopausal bleeding) among the general population of women in the United States. The findings are intended only to provide an estimate of possible evaluative procedures and associated costs related to postmenopausal bleeding that may occur after CE/BZA or CE/MPA hormone therapy initiation in the target study population.

4.5 Conclusion

Based on this exploratory modeling exercise, CE/MPA to treat moderate to severe VMS is associated with approximately 63,245 to 79,995 PMB evaluation procedures annually. Under assumptions used herein, this procedure burden may be reduced by up to 68% to 71% through the use of CE/BZA instead of CE/MPA.

This analysis indicates that the use of CE/BZA rather than CE/MPA offers an opportunity to reduce the frequency, and therefore burden, of evaluative procedures for patient and providers.

Publication Citation/Reference Used Including Funding Source of the Study

Data on file. Funding: sponsored by Pfizer.

5.0 OTHER SUPPORTING EVIDENCE

5.1 Summarizing Other Relevant Evidence

The summaries below regarding DUAVEE™ (conjugated estrogens/bazedoxifene) include information of an off-label nature. Pfizer does not suggest or recommend the use of DUAVEE™ in any manner other than as described in the Prescribing Information approved by the US Food and Drug Administration (FDA). On October 3, 2013, the FDA approved DUAVEE™ 0.45 mg/20 mg for the treatment of moderate to severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis. At that time, the FDA also issued a Complete Response Letter (CRL) declining approval of conjugated estrogens 0.524 mg/bazedoxifene 20 mg tablets in women with a uterus for the treatment of moderate to severe vulvar/vaginal atrophy (VVA) associated with menopause, for the treatment of moderate to severe vasomotor symptoms associated with menopause, and for the prevention of postmenopausal osteoporosis. The FDA determined that the data submitted were insufficient to grant approval for this indication (VVA) and dose. Pfizer is committed to working with the FDA to determine next steps.

While CE 0.45 mg/BZA 20 mg is the only FDA-approved dose, the SMART clinical trial program also evaluated CE 0.625 mg/BZA 20 mg; data for this dose are summarized in Section 3.1.2. Although not indicated for the treatment of VVA, data for this off-label use of CE/BZA are also described in Section 3.1.2. Results from the sleep/QOL substudy [17] of the SMART-5 trial [86] are summarized in Section 3.1.1.

A post hoc analysis of secondary outcomes data from the SMART-1 and SMART-2 studies was performed and will be discussed below. In addition, several health outcomes studies relating to menopause, but not specific to CE/BZA, are described below. The evidence from the following studies is summarized in the Evidence Table Spreadsheets in Section 5.1.2.

5.1.1 Published and Unpublished Studies Supporting Labeled and Off-Label Indications

Secondary Analysis of SMART-1/SMART-2 [87]

Objective

As vasomotor symptoms tend to be more severe closer to onset of menopause, secondary outcomes from the SMART-1 and SMART-2 trials were evaluated to determine whether the effects of CE/BZA are influenced by years since menopause (YSM).

Study Methods

This study was a post-hoc analysis of SMART-1 and SMART-2 (summarized in Section 3.1.1) to evaluate outcomes by YSM. The secondary outcomes assessed in the post hoc analysis were as follows:

- Frequency and severity of hot flashes (daily diary)
- Health-related QOL (MENQOL)
- Sleep (SMART-1, daily diary; SMART-2, MOS sleep scale)
- Satisfaction with treatment (MS-TSQ; SMART-2 only)
- Cumulative amenorrhea (SMART-1 only)

- Breast pain (daily diary)

Results

Subject Characteristics

Secondary outcomes were evaluated in subgroups of women who received CE 0.45 mg/BZA 20 mg (SMART-1, n = 433; SMART-2, n = 127), CE 0.625 mg/BZA 20 mg (SMART-1, n = 414; SMART-2, n = 128), or placebo (SMART-1, n = 427; SMART-2, n = 63) and were either <5 or ≥5 YSM. For SMART-1, mean age was 56.5 years, average BMI was 25.8 kg/m², and average YSM was 8.1. For SMART-2, mean age was 53.4 years, average BMI was 26.2 kg/m², and average YSM was 4.5.

Hot Flashes

In both the SMART-1 and SMART-2 trials, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg significantly decreased the average daily number of moderate to severe hot flashes and average daily hot flush severity score in both the <5 and ≥5 YSM subgroups at 3 months compared with placebo. These differences between CE/BZA and placebo were deemed of clinical importance.

Health-related QOL

CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg showed significantly greater improvement from baseline in total MENQOL scores at 3 months compared with placebo ($P \leq 0.05$), with no difference between subjects who were <5 or ≥5 YSM. Both CE/BZA doses significantly improved vasomotor function scores versus placebo ($P \leq 0.001$) irrespective of YSM. Both CE/BZA doses in the SMART-1 trial and the CE 0.625-mg/BZA 20-mg group in the SMART-2 trial significantly improved sexual function scores compared with placebo for women ≥5 YSM ($P \leq 0.05$) but not for women <5 YSM.

Sleep

In the SMART-1 trial, both the <5 and ≥5 YSM subgroups showed significant improvements in some sleep parameters with CE/BZA compared with placebo at 3 months. For subjects <5 YSM, CE 0.45 mg/BZA 20 mg significantly improved daily mean minutes slept and daily mean quality of sleep score versus placebo ($P < 0.05$ for both). For subjects ≥5 YSM, CE 0.625 mg/BZA 20 mg significantly improved daily mean quality of sleep score compared with placebo ($P < 0.01$).

In the SMART-2 trial, CE/BZA significantly improved time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II compared with placebo for both <5 and ≥5 YSM subgroups ($P < 0.05$ for all). In the ≥5 YSM subgroup, CE 0.45 mg/BZA 20 mg significantly improved somnolence and CE 0.625 mg/BZA 20 mg significantly improved time slept compared with placebo ($P < 0.05$ for both).

Satisfaction With Treatment

In the SMART-2 trial, a significantly greater percentage of CE/BZA-treated subjects in both the <5 and ≥5 YSM subgroups were satisfied with treatment overall at 3 months compared with placebo ($P < 0.05$). Both CE/BZA doses also showed significantly greater satisfaction with the ability to control hot flashes during the day and night and with quality of sleep in both the <5 and ≥5 YSM subgroups compared with placebo ($P < 0.05$). In the ≥5 YSM subgroup, CE 0.625 mg/BZA 20 mg showed significantly higher satisfaction with the effect on mood or emotions compared with placebo; in the <5 YSM subgroup, both

CE/BZA doses showed significantly better satisfaction with tolerability of side effects versus placebo ($P < 0.05$ for all).

Amenorrhea

In the SMART-1 trial, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg were associated with high rates of cumulative amenorrhea not significantly different from those for placebo; no differences were observed between < 5 and ≥ 5 YSM subgroups.

Breast Pain

Rates of breast pain were low in both studies and not significantly different from placebo in both the < 5 and ≥ 5 YSM subgroups.

Conclusions

For the majority of secondary outcomes, results did not typically differ for women < 5 and ≥ 5 YSM when comparing CE/BZA with placebo. This finding suggests that CE/BZA is an effective menopausal therapy for women who have recently reached menopause, as well as for women who are ≥ 5 years past menopause onset.

Health Resource Utilization Associated With Breast Pain/Endometrial Bleeding and Hormone Therapy [87]

Objective

This retrospective study examined the incremental total health care costs for subjects prescribed HT who had breast pain and/or endometrial bleeding in a US managed care setting.

Study Methods

This was a retrospective study that identified 2 mutually exclusive cohorts: subjects in the Selected AEs Cohort had evidence of ≥ 1 occurrence of breast pain or endometrial bleeding during the post-index date period, and patients in the No Selected AEs Cohort had no evidence of breast pain and/or endometrial bleeding during the post-index date period. The 2 cohorts were selected using the MarketScan Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits Databases from October 2005 to September 2010.

Inclusion criteria

- Females aged 45 to 65 years
- Prescribed HT from January 1, 2006 to September 30, 2008
- Continuously enrolled in a health plan with medical and pharmacy benefits for ≥ 1 quarter before (pre-index period) and after the index date (post-index period; index date was date of first HT prescription)

Exclusion criteria

- Evidence of HT prescription during the pre-index period
- Evidence of pregnancy
- Evidence of breast cancer
- Evidence of hysterectomy
- Evidence of breast pain and/or endometrial bleeding during the pre-index period

Results*Patient Characteristics*

A total of 55,267 subjects were selected for inclusion; of these, 5,325 (9.64%) had evidence of breast pain and/or endometrial bleeding (Selected AEs Cohort) and 49,942 had no evidence of breast pain and/or endometrial bleeding (No Selected AEs Cohort). Among subjects with selected AEs, 84% (n = 4,469) had endometrial bleeding only, 14% (n = 751) had breast pain only, and 2% (n = 105) had both.

Total Health Care Costs

During the post-index period, subjects in the Selected AEs Cohort had significantly higher quarterly costs compared with the No Selected AEs for the following measures:

- Total health care costs (\$2,102 vs \$1,835; $P < 0.001$)
- Outpatient physician visit costs (\$152 vs \$118; $P < 0.001$)
- Other outpatient costs (\$1,075 vs \$804; $P < 0.001$)
- Transvaginal ultrasound (\$18 vs \$2; $P < 0.001$)
- Endometrial biopsy (\$13 vs \$0; $P < 0.001$)

After controlling for demographic and clinical covariates between cohorts, adjusted quarterly total health care costs for the Selected AEs Cohort ranged from \$1,944 to \$2,185 and for the No Selected AEs Cohort from \$1,699 to \$1,971. Quarterly health care cost differences between cohorts were from \$250 at first quarter to \$214 at eighth quarter ($P < 0.0001$ for both).

For annual costs, the increment total health care cost for the Selected AEs Cohort was \$1,003 in the first year and \$911 in the second year. When averaged on an annual basis, the cost difference was \$957 higher for subjects in the Selected AEs Cohort ($P < 0.001$). Please see **Table 5.1** for a summary of health care costs broken down by cohort and quarter.

Table 5.1. Adjusted Health Care Costs, P-value, and Effect Size Among Selected AE Cohort Versus No Selected AE Cohort

All patients	Selected AE cohort (n = 3,856)		No selected AE cohort (n = 29,803)		P-value	Effect size
	Mean	SD	Mean	SD		
Quarterly post-index health care costs						
Q1	\$2,121	\$1,301	\$1,871	\$1,291	<0.0001	19
Q2	\$1,944	\$1,252	\$1,699	\$1,237	<0.0001	20
Q3	\$1,997	\$1,275	\$1,742	\$1,217	<0.0001	20
Q4	\$2,007	\$1,281	\$1,754	\$1,219	<0.0001	20
Q5	\$2,048	\$1,286	\$1,804	\$1,240	<0.0001	19
Q6	\$2,024	\$1,304	\$1,796	\$1,246	<0.0001	18
Q7	\$2,064	\$1,334	\$1,839	\$1,255	<0.0001	17
Q8	\$2,185	\$1,461	\$1,971	\$1,300	<0.0001	15
First year of follow-up health care costs	\$8,069	\$2,555	\$7,066	\$2,483	<0.0001	20
Second year of follow-up health care costs	\$8,321	\$2,696	\$7,410	\$2,521	<0.0001	15
Average annual follow-up health care costs	\$8,195	\$1,857	\$7,238	\$1,769	<0.0001	20

AE, adverse event; SD, standard deviation; Q, quarter.

Conclusions

Endometrial bleeding and breast pain generated higher costs in patients who were prescribed HT. After matching the cohorts, this study estimated incremental total healthcare costs associated with endometrial bleeding and breast pain at \$239 quarterly and \$957 annually, in a US managed care setting.

Burden of Menopausal Symptoms: Analysis of Health Care Resource Utilization Using the Medical Expenditure Panel Survey [88]

Objective

This study explored the relative cost burden associated with menopausal symptoms compared with other chronic conditions using data from women in the 2009 Medical Expenditure Panel Survey (MEPS). [88]

Study Methods

This retrospective study calculated the economic burden of self-reported menopausal symptoms, as well as other chronic conditions, and compared results to controls (ie, females who reported none of these medical conditions during the study period).

Inclusion criteria

- Women aged 45 to 65 years in the 2009 MEPS
- No history of hysterectomy
- Presence of self-reported menopausal symptoms (as defined by MEPS classification code) of osteoporosis, fibromyalgia, overactive bladder, depression, or cardiovascular disease

Subjects with >1 of the chronic conditions in the inclusion criteria were excluded from this study

Results*Patient Characteristics*

A total of 1,108 subjects were included in the analysis: controls (n = 411), menopausal symptoms (n = 77), osteoporosis (n = 55), fibromyalgia (n = 241), overactive bladder (n = 9), depression (n = 294), cardiovascular disease (n = 21). Mean age was 53.4 years and 47% of the population was white.

Health Care costs

Annual adjusted per-patient direct health care costs in women with menopausal symptoms were significantly higher versus controls (estimated adjusted difference from controls, 72.1; $P < 0.0001$) but were not significantly different than women with osteoporosis (-29.9; $P = 0.4152$), depression (20.3; $P = 0.5553$), or overactive bladder (116.5; $P = 0.3717$) [87]. Please see **Table 5.2** for a summary of health care costs.

Table 5.2. Adjusted Annual Per-Patient Direct Health Care Costs From MEPS 2009 [87]

Condition	Estimated* difference from controls		Estimated* difference from menopausal symptoms	
	Annual direct health care costs	P-value	Annual direct health care costs	P-value
Menopausal symptoms	\$72.10	<0.0001	-	-
Osteoporosis	\$42.30	0.0072	-\$29.90	0.4152
Fibromyalgia	\$488.00	<0.0001	\$415.90	<0.0001
Depression	\$92.50	<0.0001	\$20.30	0.5553
Overactive bladder	\$188.60	0.0107	\$116.50	0.3717
Cardiovascular disease	\$532.50	<0.0001	\$460.40	0.0053

MEPS, Medical Expenditure Panel Survey.

*Adjusted for age, race, ethnicity, insurance status, education level, and income.

Conclusions

Among a sample of women from the 2009 MEPS, women experiencing menopausal symptoms had significantly higher annual direct healthcare costs than those of controls and had comparable annual direct healthcare costs to those associated with osteoporosis, depression, and overactive bladder.

Publication Citation/Reference Used Including Funding Source of the Study

Chandran A, Joyce Nina, Bushmakin AG, Louie MJ, Assaf AR. Burden of Menopausal Symptoms Using the Medical Expenditure Panel Survey (MEPS). Oral presentation presented at: the NAMS 24th Annual Meeting; October 9-12, 2013; Dallas, TX 2013. Funding: sponsored by Pfizer.

Quality of Life, Menopausal Symptom Burden, and Discontinuation Rates and Causes Associated With HT: Results from a US Survey [89]

Objective

This study evaluated treatment discontinuation rates and causes, health-related QOL, and menopausal symptoms reported by women prescribed HT between January 1, 2007 and December 31, 2011.

Study Methods

This one-time mail survey was administered to female patients of the Reliant Medical Group in Worcester, MA. Participants were identified from administrative claims data.

Inclusion criteria

- Women aged 45 to 64 years
- Filled ≥ 1 month's supply of oral or transdermal HT between January 1, 2007 and December 31, 2011
- No history of breast cancer, VTE, stroke, gynecological cancer, or hysterectomy in available data
- Enrolled in the Fallon Community Health Plan with a Reliant Medical Group primary care physician as of the date of survey administration

Results

Patient Characteristics

Among 704 surveys mailed, 265 (37.6%) surveys were returned and 72 respondents met eligibility criteria. The majority of respondents were white (96%), with a mean age of 60 years; 58% of the study sample was prescribed HT for ≥ 3 years.

HT Patterns of Use

Prior to starting HT therapy, most (93%) respondents expected to benefit from HT and approximately one-third reported concern about side effects. At the time of the survey, 63% of respondents were no longer taking HT; most common reasons for discontinuation were "doctor told me to stop" (73%), "concerned could cause side effects" (27%), or "side effects bothered me" (18%; see **Table 5.3**).

Table 5.3. Reasons for Discontinuation of HT

	Percent* among those discontinuing HT (N = 45)
Doctor told me to stop	73%
Concerned they can cause side effects	27%
The side effects bothered me	18%
They didn't adequately relieve my hot flushes/night sweats	16%
They cost too much	11%
Other	22%

HT, hormone therapy.

*Respondents may have indicated more than 1 reason; therefore, proportions of respondents do not total 100%.

Health-related QOL

QOL was numerically higher among those currently taking HT compared with those not taking HT (mean EQ-5D score, 0.86 vs 0.83, respectively; see **Table 5.4**).

Menopausal Symptoms

Most individual symptoms were less severe in respondents currently taking HT. Rates of “severe” or “very severe” hot flushes/night sweats were 12% versus 22% and “severe” or “very severe” vaginal dryness were 4% versus 20% for respondents currently taking HT compared with those who discontinued, respectively. Mean total Menopausal Rating Scale (MRS) score was lower for respondents taking HT compared with those not currently taking HT (8 vs 12, respectively; see **Table 5.4**).

Table 5.4. QOL and Symptom Severity: Comparison of Those Taking HT With Those Not Taking HT

	Currently taking HT (n = 27)	Not currently taking HT (n = 45)
EQ-5D index scores*	0.86	0.83
Mean current MRS score†		
Total MRS score	8	12
Psychological symptoms	4	5
Somato-vegetative symptoms	3	5
Urogenital symptoms	3	4

QOL, quality of life; HT, hormone therapy; MRS, Menopausal Rating Scale.

*The EQ-5D is a standardized measure of health status scored on a scale of -0.11 to 1.0, with higher scores indicating greater QOL [70].

†The MRS is a standardized measure of types and severity of current menopausal symptoms which is scored on a scale of 0-44, with higher scores indicating greater symptom burden [91].

Conclusions

Rates of HT discontinuation were high among this group of women. Reasons for discontinuation included concern about potential side effects or having been bothered by side effects. Women who were on therapy during the survey reported higher health-related QOL, less burden from menopausal symptoms and were less likely to report having “severe” or “very severe” menopausal symptoms.

Publication Citation/Reference Used Including Funding Source of the Study

Trocio J, Mirkin S, Sussman M, Best C, Chandran A, Louie M, Bushmakin A, Yood R, Friedman M, Menzin J. Hormonal Therapy Treatment, Quality of Life and Menopausal Symptom Burden among Mid-Life Women: Implications of Medication Discontinuation. Oral presentation presented at: the NAMS 24th Annual Meeting; October 9-12, 2013; Dallas, TX 2013. Funding: sponsored by Pfizer.

National Health & Wellness Survey Analyses – 2005: Impact of Menopausal Symptoms on QOL, Productivity, and Economic Outcomes [90]

Objective

The objective of this study was to evaluate the impact of menopausal symptoms on health-related QOL and productivity, and to quantify the economic burden based on data from the 2005 US National Health & Wellness Survey (NHWS).

Study Methods

Data were obtained from the 2005 NHWS, the most recent NHWS survey that assessed menopausal symptoms. The NHWS is a self-administered internet-based questionnaire that uses a stratified random sampling procedure to ensure samples are representative of the demographic composition of the general US adult population. From the overall NHWS 2005 sample, those meeting the inclusion criteria below were included in this study.

Inclusion criteria

- Females aged 40 to 64 years (inclusive)
- No history of cancer
- Provided data on menopausal symptoms experience

Results

Patient Characteristics

A total of 8,811 subjects met the eligibility criteria and were included in the analysis. Mean age was 49.8 years, 89.0% were white, and lifetime prevalence of HT use was 30.6% (11.3% were current HT users). Lifetime prevalence of depression medication use was 24.0%, with 17.6% currently taking antidepressants.

Burden of Menopausal Symptoms

A total of 4,116 (46.7%) of women in the sample had ≥ 1 of the listed menopausal symptoms, which included anxiety, decreased interest in sex, depression, forgetfulness, heart racing or pounding, hot flashes, insomnia/difficulty sleeping, joint stiffness, mood changes, night sweats, urine leakage, or vaginal dryness.

Health-related QOL

After adjusting for differences in demographics and health characteristics, presence of menopausal symptoms was associated with significantly lower mental (45.8 vs. 47.4) and physical health-related QOL (46.8 vs 48.6) compared with women not experiencing menopausal symptoms ($P < 0.05$ for both; see **Table 5.5** for adjusted SF-8 scale scores).

Productivity and Health Care Utilization

Women experiencing menopausal symptoms reported significantly higher presenteeism (percentage of impairment while at work due to health in the past 7 days; 17.7% vs 13.6%; $P < 0.05$) and overall work impairment (16.1% vs 12.3%; $P < 0.05$) than women not experiencing menopausal symptoms, but absenteeism was similar between groups (3.7% vs 3.4%; $P = 0.50$). Women with menopausal symptoms had significantly higher impairment in daily activities (28.1% vs 23.3%; $P < 0.05$) and significantly more physician visits in the past 6 months (2.1 vs 1.9; $P < 0.05$) compared with women without menopausal symptoms, but number of emergency room visits (0.19 vs 0.17; $P = 0.05$) and hospitalizations (0.24 vs 0.22; $P = 0.40$) was similar (see **Table 5.5**).

Table 5.5. Adjusted QOL, Work Impairment, and Health Care Resource Utilization: Comparison of Those With and Without Menopausal Symptoms

	Menopausal symptoms (n = 4,116)	No menopausal symptoms (n = 4,695)	P-value
QOL (SF-8 score[*])			
Mental component	45.8	47.4	<0.05
Physical component	46.8	48.6	<0.05
Work impairment (WPAI score[†])			
Presenteeism	17.7%	13.6%	<0.05
Overall work impairment	16.1%	12.3%	<0.05
Absenteeism	3.7%	3.4%	0.50
Impairment in daily activities	28.1%	23.3%	<0.05
Health care resource utilization			
Mean physician visits	2.1	1.9	<0.05
Mean ER visits	0.19	0.17	0.05
Mean days hospitalized	0.24	0.22	0.40

QOL, quality of life; WPAI, Work Productivity and Activity Impairment; ER, emergency room.

^{*}The SF-8 is a standardized measure for self-reported health status and well-being, with higher scores indicating better health status [90].

[†]The WPAI is a standardized measure of work and activity impairment during the past 7 days where the scale ranges from 0% to 100%, with higher values indicating greater impairment [70].

Burden of Specific Menopausal Symptoms

The mean number of menopausal symptoms was 4.8. The most common symptoms among those reporting menopausal symptoms were as follows:

- Hot flashes (87.4%)
- Night sweats (66.6%)
- Insomnia/difficulty sleeping (60.1%)
- Forgetfulness (49.5%)
- Mood changes (48.3%)
- Decreased interest in sex (44.7%)

Based on regression models, depression, anxiety, heart racing, and forgetfulness were the symptoms with the strongest effects on health-related QOL and activity impairment. Joint stiffness was the only symptom significantly associated with overall work impairment. Vaginal dryness, depression, and forgetfulness were significantly associated with increased physician visits, and night sweats, mood changes, and depression were significantly associated with increased number of emergency room visits.

Conclusions

In this population, women experiencing menopausal symptoms reported significantly lower mental and physical health-related QOL as well as significantly higher presenteeism, overall work impairment, impairment in daily activities and healthcare utilization than women without menopausal symptoms.

Publication Citation/Reference Used Including Funding Source of the Study

Whiteley J, DiBonaventura M, Wagner JS, Alvir J, Shah S. The Impact of Menopausal Symptoms on Quality of Life, Productivity, and Economic Outcomes. *J Womens Health* 2013; 22(11). Funding: sponsored by Pfizer.

NHWS Analyses – 2005: Cross-sectional Study of Depression, QOL, Work Productivity, Resource Use, and Costs Among Women Experiencing Menopause and Hot Flashes [69]

Objective

The objective of this study was to evaluate the impact of depression on health-related QOL and productivity, and health care resource utilization and costs among women experiencing menopausal symptoms with hot flashes, based on data from the US 2005 NHWS.

Study Methods

Data were obtained from the 2005 NHWS, the most recent NHWS survey that assessed menopausal symptoms. The NHWS is a self-administered, cross-sectional, internet-based survey that uses a stratified random sampling procedure to ensure samples are representative of the demographic composition of the general US adult population. From the overall NHWS 2005 sample, those meeting the inclusion criteria were included in this study. Women reporting depression in the past 12 months were compared with women not reporting depression in the past 12 months.

Inclusion criteria

- Females aged 40 to 64 years (inclusive)
- No history of cancer or bipolar disorder
- Presence of menopausal symptoms with hot flashes

Results*Patient Characteristics*

A total of 3,632 women met eligibility criteria and were included in the analysis. Of these, 1,165 (32.1%) reported experiencing depression and 2,467 (67.9%) did not report experiencing depression. Subjects experiencing depression were significantly more likely to be aged 40 to 44 years or 45 to 49 years, white, unmarried, current smokers, obese, and not exercising ($P < 0.05$ for all).

Adjusted Health-related QOL, Work Productivity, and Resource Use

After controlling for differences in demographics and health risks, women with menopausal symptoms and depression had significantly worse health outcomes than women with menopausal symptoms without depression, including lower mental and physical health-related QOL; greater levels of absenteeism, presenteeism, and activity impairment; and higher numbers of physician visits, emergency room visits, and days hospitalized ($P < 0.05$ for all; see **Table 5.6**).

Table 5.6. Adjusted QOL, Work Impairment, and Health Care Resource Utilization Among Women Reporting Menopausal Symptoms with Hot Flashes: Comparison of Those With and Without Depression

	Depression (n = 1,165)	No depression (n = 2,467)	P-value
Quality of life (SF-8 score[*])			
Mental component	39.66	50.85	<0.05
Physical component	44.05	46.38	<0.05
Work impairment (WPAI score[†])			
Presenteeism	25.00%	14.32%	<0.05
Absenteeism	5.31%	2.80%	<0.05
Impairment in daily activities	37.32%	23.16%	<0.05
Health care resource utilization			
Mean physician visits	2.47	1.77	<0.05
Mean ER visits	0.27	0.16	<0.05
Mean days hospitalized	0.36	0.18	<0.05

QOL, quality of life; WPAI, Work Productivity and Activity Impairment; ER, emergency room.

^{*}The SF-8 is a standardized measure for self-reported health status and well-being, with higher scores indicating better health status [90].

[†]The WPAI is a standardized measure of work and activity impairment during the past 7 days where the scale ranges from 0% to 100%, with higher values indicating greater impairment [70].

Indirect and Direct Costs

Indirect (\$7,650 vs \$4,584 per employed woman per year; $P < 0.0001$) and direct costs (\$2,642 vs \$1,567 per woman per year; $P < 0.0001$) were significantly higher for women experiencing depression than for those without depression (see **Table 5.7**).

Table 5.7. Annual Direct and Indirect Costs: Comparison of Those With and Without Depression

	Depression (n = 1,165)	No depression (n = 2,467)	P-value
Direct costs *	\$2,642	\$1,567	<0.0001
Indirect costs †	\$7,650	\$4,584	<0.0001

*Direct costs include physician visits, emergency room visits, and days hospitalized.

†Indirect costs include lost income due to presenteeism and absenteeism.

Conclusions

Among women in this study experiencing menopausal symptoms, approximately one-third reported experiencing depression. Women experiencing both menopausal symptoms and depression reported significantly worse QOL and significantly greater work productivity loss, healthcare resource use, and costs.

Publication Citation/Reference Used Including Funding Source of the Study

Dibonaventura MD, Wagner JS, Alvir J, Whiteley J. Depression, quality of life, work productivity, resource use, and costs among women experiencing menopause and hot flashes: a cross-sectional study. *Prim Care Companion CNS Disord.* 2012;14(6). Funding: sponsored by Pfizer.

NHWS Analyses – 2010: Impact of Presence and Severity of VMS on Health Status, Productivity, and Health Care Resource Use and Costs [70]**Objective**

The objective of this study was to evaluate the impact of the presence and severity of VMS on health status, productivity, and health care resource use and costs based on data from the 2010 US NHWS.

Study Methods

Data were obtained from the 2010 NHWS, an annual, cross-sectional, self-administered, internet-based survey. The NHWS uses a stratified random sampling procedure to ensure samples are representative of the demographic composition of the general US adult population. From the overall NHWS 2010 sample, women aged 40 to 75 years were contacted via email to participate in an additional internet survey.

Inclusion criteria

- Females aged 40 to 75 years from the NHWS
- No menstrual bleeding or spotting for ≥ 1 year

Results

Patient Characteristics

A total of 3,267 postmenopausal women were stratified by VMS severity: none (n = 1,740), mild (n = 931), moderate (n = 462), and severe (n = 134). More than half (53.6%) of the women included were aged 60 to 75 years, 37.2% were aged 50 to 59 years, and the remaining 9.2% were aged 40 to 49 years. Only 8.5% reported ever using HT and 16.6% had a diagnosis of osteoporosis.

Work Productivity Loss

Among employed women experiencing VMS, increasing severity was associated with an increase in adjusted mean level of presenteeism (4.04% [mild] vs 14.46% [moderate] vs 24.28% [severe]; $P < 0.0001$) and overall work impairment (4.33% [mild] vs 14.30% [moderate] vs 24.56% [severe]; $P < 0.0001$). In women with VMS regardless of employment, increasing VMS severity was associated with an increase in adjusted mean level of activity impairment (6.16% [mild] vs 17.06% [moderate] vs 31.66% [severe]; $P < 0.0001$; see **Table 5.8**).

Health Status

Increasing VMS severity was associated with a decrease in health status; women experiencing severe and moderate VMS had significantly lower mean health status scores compared with women with no symptoms ($P < 0.0001$; see **Table 5.8**).

Resource Use

Adjusted mean number of menopause symptom-related physician visits was significantly higher for women with severe, moderate, and mild VMS symptoms than for women with no symptoms ($P < 0.0001$; see **Table 5.8**).

Table 5.8. Adjusted QOL, Work Impairment, and Health Care Resource Utilization by VMS Severity

	None (n = 1,740)	Mild (n = 931)	Moderate (n = 462)	Severe (n = 134)	P-value
QOL (EQ-5D score [*])	0.86	0.85	0.82	0.77	<0.0001 [†]
Work impairment (WPAI score [‡])					
Presenteeism		4.04%	14.46%	24.28%	<0.0001
Overall work impairment		4.33%	14.30%	24.56%	<0.0001
Impairment in daily activities		6.16%	17.06%	31.66%	<0.0001
Mean menopause-related physician visits	0.73	1.63	2.37	2.73	<0.0001

QOL, quality of life; VMS, vasomotor symptoms; WPAI, Work Productivity and Activity Impairment.

^{*}The EQ-5D is a standardized measure of health status scored on a scale of -0.11 to 1.0, with higher scores indicating greater quality of life [70].

[†]Moderate or severe VMS vs no symptoms.

[‡]The WPAI is a standardized measure of work and activity impairment during the past 7 days where the scale ranges from 0% to 100%, with higher values indicating greater impairment [70].

Health Outcomes Stratified by Years Since FMP

As a post hoc analysis, effects of VMS severity on health outcomes were evaluated among women <5 years since FMP and for women 5 to 10 years since FMP. Effects of no VMS and mild VMS were similar for women <5 years since FMP and 5 to 10 years since FMP. Effects of moderate and severe VMS were more detrimental for women 5 to 10 years since FMP, who reported lower health status, higher overall work impairment and more menopause-related physician visits than women <5 years since FMP.

Cost Analyses

Costs associated with observed presenteeism, overall work impairment, and menopause-related physician visits increased with severity of VMS (see **Table 5.9**).

Table 5.9. Annual Direct and Indirect Costs by VMS Severity

	None (n = 1,740)	Mild (n = 931)	Moderate (n = 462)	Severe (n = 134)
Direct costs				
Associated with menopause-related physician visits	\$257	\$574	\$834	\$961
Indirect costs				
Associated with presenteeism		\$1,079	\$3,595	\$6,584
Associated with overall work impairment		\$1,156	\$3,819	\$6,559

VMS, vasomotor symptoms.

Conclusions

Among postmenopausal women in this study, greater VMS severity is significantly associated with lower reported health status and work productivity as well as greater healthcare resource use.

Publication Citation/Reference Used Including Funding Source of the Study

Whiteley J, Wagner JS, Bushmakin A, Kopenhafer L, Dibonaventura M, Racketta J. Impact of the severity of vasomotor symptoms on health status, resource use, and productivity. *Menopause*. 2013;20(5):518-524. Funding: sponsored by Pfizer.

WHPI Burden of Illness Study [85]

Objective

The objective of this study was to estimate the prevalence of individual and coexisting conditions (chronic joint and muscular pain [“pain”], urinary incontinence [UI], major depressive disorder [MDD], osteoporosis risk, moderate/severe VMS, and VVA), their associated health status, and patterns of health-seeking behavior related to each condition. The study was conducted via a telephone survey of women in the United States between October 2012 and January 2013.

Study Methods

This cross-sectional, prospective study collected data from a nationally representative sample of women in the United States using the EXCEL Omnibus Survey, which is a national telephone survey conducted by Social Science Research Solutions (SSRS).

Inclusion criteria

- English-speaking or Spanish-speaking women
- Aged 40 to 64 years
- Selected from both landline and cellular random digit dialing samples

Results

Patient Characteristics

A total of 3,058 women completed the survey. Mean age was 53.4 years, with 69.8% having self-reported menopause and 8.3% on ET. Of those women surveyed, 35.2% did not have any of the 6 conditions, 34.2% had 1 condition, 17.9% had 2 conditions, and 12.7% had ≥ 3 conditions. Prevalence rates for the 6 conditions are shown in **Table 5.10**.

Table 5.10. Menopausal Symptom Prevalence Rates: Single and By Number of Conditions

	Prevalence, % (95% CI)
Single prevalence rates*	
Osteoporosis risk	30.6 (28.8-32.4)
VVA	27.8 (25.9-29.8)
UI	26.6 (25.1-28.2)
Pain	17.0 (15.6-18.3)
MDD	12.6 (11.4-13.8)
Moderate/severe VMS [87]	13.7 (12.4-14.9)
Number of conditions	
No conditions	35.2 (33.5-36.9)
At least 1 condition	64.81 [†]
At least 2 conditions	30.6 [†]
3 or more conditions	12.7 (11.5-13.9)

CI, confidence interval; VVA, vulvar/vaginal atrophy; UI, urinary incontinence; MDD, major depressive disorder; VMS, vasomotor symptoms.

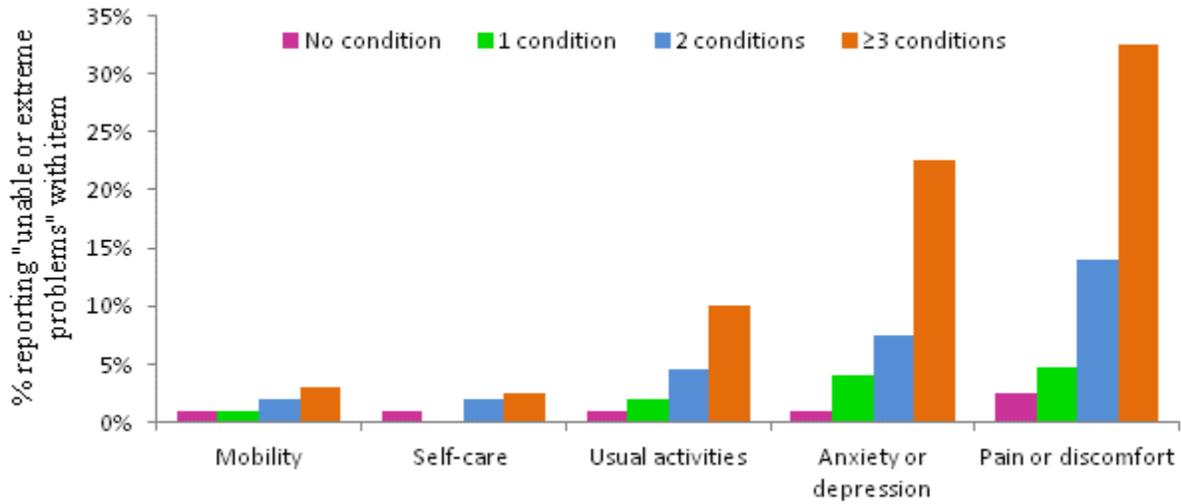
*All sample sizes >1,800.

[†]CI not available.

Health Status

Health status declined significantly with each added condition (pairwise $P < 0.01$). Health status also differed significantly between women with and without each of the 6 conditions ($P < 0.01$); except for osteoporosis risk, the presence of any of the 6 conditions was associated with lower perceived health status versus the absence of the condition. The proportion of women reporting “unable or extreme problems” for each EQ-5D dimension increased with additional conditions (**Figure 5.1**). The proportion of women reporting no problems, some or moderate problems, or unable or extreme problems was significantly different in women with or without each condition ($P < 0.01$).

Figure 5.1. Extreme problems with EQ-5D Health Status Dimensions by number of conditions.



Health-Seeking Behavior

For those women who screened positive for a given condition, the percent who discussed it with her doctor ranged from 40.3% (VVA) to 89.7% (MDD), while those reporting treatment for the condition ranged from 13.1% (osteoporosis risk) to 69.2% (pain).

Conclusions

Over 25% of women aged 40 to 64 years in this survey had multiple coexisting women’s health conditions. Having multiple conditions was associated with worsening general health status, which declined with each added condition.

Publication Citation/Reference Used Including Funding Source of the Study

Lang K, Alexander I, Simon J, et al. Burden of illness associated with selected health conditions among women aged 40-64 years: findings from a U.S. nationally-representative survey. Poster presented at: Women’s Health 2013: The 21st Annual Congress; March 22-24, 2013; Washington, DC. Funding was sponsored by Pfizer.

5.1.2 Evidence Table Spreadsheets

Table 5.11. Evidence Table of Other Supporting Evidence for CE/BZA

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
SMART-1/ SMART-2 Secondary outcomes [87] Secondary analysis	Outpatient, randomized, double-blind, PBO- controlled, phase 3 studies Secondary outcomes by YSM	SMART-1: Healthy, postmenopausal women aged 40- 75 years with an intact uterus and acceptable endometrial biopsy results at screening SMART-2: Healthy, postmenopausal women aged 40- 65 years with an intact uterus and ≥7 moderate to severe hot flushes per day (or ≥50 per week) at screening	SMART-1: CE 0.45 mg/BZA 20 mg (n = 433) CE 0.625 mg/BZA 20 mg (n = 414) PBO (n = 427) SMART-2: CE 0.45 mg/BZA 20 mg (n = 127) CE 0.625 mg/BZA 20 mg (n = 128) PBO (n = 63)	<ul style="list-style-type: none"> • Frequency and severity of hot flushes (daily diary) • Health-related QOL (MENQOL) • Sleep (SMART-1, daily diary; SMART-2, MOS sleep scale) • Satisfaction with treatment (MS-TSQ; SMART-2 only) • Cumulative amenorrhea (SMART-1 only) • Breast pain (daily diary) 	<p>Hot flushes In both SMART-1 and SMART-2, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg significantly decreased average daily number of moderate to severe hot flushes and average daily hot flush severity score in both <5 and ≥5 YSM subgroups at 3 months vs PBO</p> <p>Health-related QOL</p> <ul style="list-style-type: none"> • CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg showed significantly greater improvement from baseline in total MENQOL scores at 3 months vs PBO ($P \leq 0.05$), with no significant difference between <5 or ≥5 YSM • Both CE/BZA doses significantly improved vasomotor function scores vs PBO ($P \leq 0.001$) irrespective of YSM • Both CE/BZA doses in SMART-1 and CE 0.625 mg/BZA 20 mg in SMART-2 significantly improved sexual function scores vs PBO for women ≥5 YSM ($P \leq 0.05$) but not <5 YSM <p>Sleep</p> <ul style="list-style-type: none"> • In SMART-1, for subjects <5 YSM, CE 0.45 mg/BZA 20 mg significantly improved daily mean minutes slept and daily mean quality of sleep score vs PBO ($P < 0.05$ for both); for subjects ≥5 YSM, CE 0.625 mg/BZA 20 mg significantly improved daily mean quality of sleep score vs PBO ($P < 0.01$) • In SMART-2, CE/BZA significantly improved time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II vs PBO for both <5 and ≥5 YSM subgroups ($P < 0.05$ for all); in ≥5 YSM subgroup, CE 0.45 mg/BZA 20 mg significantly improved somnolence and CE 0.625 mg/BZA 20 mg significantly improved time slept vs PBO ($P < 0.05$ for both) <p>Satisfaction with treatment</p> <ul style="list-style-type: none"> • In SMART-2, significantly greater percentage of CE/BZA-treated subjects in both <5 and ≥5 YSM subgroups were satisfied with treatment overall at 3 months vs PBO ($P < 0.05$) • Both CE/BZA doses showed significantly greater satisfaction with ability to control hot flushes during the day and night and quality of sleep in both <5 and ≥5 YSM vs PBO ($P < 0.05$) • In ≥5 YSM subgroup, CE 0.625 mg/BZA 20 mg

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
					<p>showed significantly higher satisfaction with effect on mood or emotions vs PBO; in the <5 YSM subgroup, both CE/BZA doses showed significantly better satisfaction with tolerability of side effects vs PBO ($P < 0.05$ for all).</p> <p>Amenorrhea In SMART-1, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg had high rates of cumulative amenorrhea not significantly different from PBO; no differences were observed between <5 and ≥ 5 YSM subgroups</p> <p>Breast pain Rates of breast pain were low in both studies and not significantly different from placebo in both <5 and ≥ 5 YSM subgroups</p>
<p>Health Resource Utilization Associated With Breast Pain/Endometrial Bleeding and HT [87]</p> <p>US managed care setting</p>	<p>Retrospective cohort study of 2 mutually exclusive cohorts:</p> <p>Selected AEs Cohort, ≥ 1 occurrence of breast pain or endometrial bleeding</p> <p>No Selected AEs Cohort, no evidence of breast pain and/or endometrial bleeding</p>	<p>Females aged 45-65 years prescribed HT from January 1, 2006 to September 30, 2008 with continuous enrollment in a health plan with medical and pharmacy benefits (N = 55,267)</p> <p>Selected AEs Cohort (n = 5,325)</p> <p>No Selected AEs Cohort (n = 49,942)</p>	HT	<p>Total health care costs, including inpatient, outpatient physician visit, outpatient pharmacy, outpatient ER visit, and other outpatient costs</p>	<p>Total health care costs</p> <ul style="list-style-type: none"> Subjects in Selected AEs Cohort had significantly higher quarterly total health care costs (\$2,102 vs \$1,835; $P < 0.001$), outpatient physician visit costs (\$152 vs \$118; $P < 0.001$), and other outpatient costs (\$1,075 vs \$804; $P < 0.001$) vs the No Selected AEs Cohort Selected AEs Cohort had significantly higher quarterly costs for transvaginal ultrasound (\$18 vs \$2; $P < 0.001$) and endometrial biopsy (\$13 vs \$0; $P < 0.001$) vs No Selected AEs Cohort <p>Multivariate analysis</p> <ul style="list-style-type: none"> Adjusted quarterly total health care costs for Selected AEs Cohort ranged from \$1,944 to \$2,185 and for No Selected AEs Cohort from \$1,699 to \$1,971 Quarterly health care cost differences between cohorts were from \$250 at first quarter to \$214 at eighth quarter ($P < 0.0001$ for both) For annual costs, increment total health care costs for Selected AEs Cohort was \$1,003 in the first year and \$911 in the second year; when averaged on an annual basis, cost difference was \$957 higher for subjects in Selected AEs Cohort ($P < 0.001$)

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
Burden of Menopausal Symptoms: Analysis of Health Care Resource Utilization Using the MEPS [88]	Retrospective study of economic burden of self-reported menopausal symptoms and other chronic conditions vs controls (ie, females who reported none of these medical conditions during the study period)	Women aged 45-65 years in the 2009 MEPS with no history of hysterectomy and presence of 1 of the following: menopausal symptoms, osteoporosis, fibromyalgia, overactive bladder, depression, or cardiovascular disease (N = 1,108)	N/A	Economic burden: direct costs, including total expenditures and total charges for inpatient, outpatient, and ER medical events	<ul style="list-style-type: none"> Annual adjusted direct health care costs in women with menopausal symptoms were significantly higher vs control (estimated adjusted difference from controls, 72.1; $P < 0.0001$) but not significantly different than women with osteoporosis (-29.9; $P = 0.4152$), depression (20.3; $P = 0.5553$), or overactive bladder (116.5; $P = 0.3717$)
Quality of Life, Menopausal Symptom Burden, and Discontinuation Rates and Causes Associated With HT: Results from a US Survey [89]	One-time mail survey of female patients of the Reliant Medical Group in Worcester, MA identified from administrative claims data to evaluate discontinuation rates and causes, health-related QOL, and menopausal symptoms reported by women prescribed HT	Women aged 45-64 years who filled ≥ 1 month's supply oral or transdermal HT between January 1, 2007 and December 31, 2011 (N = 72)	HT	<ul style="list-style-type: none"> HT patterns of use Health-related QOL (EQ-5D) Menopausal symptom frequency and severity (MRS) 	<p>HT patterns of use</p> <ul style="list-style-type: none"> Prior to starting HT, most (93%) respondents expected to benefit from HT and approximately one-third reported concern about side effects At the time of survey, 63% were no longer taking HT; most common reasons for discontinuation were "doctor told me to stop" (73%), "concerned could cause side effects" (27%), or "side effects bothered me" (18%) <p>Health-related QOL</p> <p>QOL was numerically higher among those currently taking HT vs those not taking HT (mean EQ-5D score, 0.86 vs 0.83, respectively)</p> <p>Menopausal symptoms</p> <ul style="list-style-type: none"> Most individual symptoms were less severe in respondents currently taking HT Rates of "severe" or "very severe" hot flushes/night sweats were 12% vs 22% and "severe" or "very severe" vaginal dryness were 4% vs 20% for respondents currently taking HT vs those who discontinued, respectively Mean total MRS score was lower for respondents taking HT vs those not taking HT (8 vs 12, respectively)

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
<p>NHWS – 2005: Impact of Menopausal Symptoms on QOL, Productivity, and Economic Outcomes [90]</p> <p>US</p>	<p>Data obtained from 2005 NHWS, a self-administered internet-based questionnaire representative of US adult population, were used to determine the impact of menopausal symptoms on health-related QOL and productivity and to quantify economic burden</p>	<p>Females aged 40-64 years with no history of cancer who provided data on menopausal symptoms experience (N = 8,811)</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Self-reported menopausal symptoms • Health-related QOL (SF-8) • Work productivity (WPAI questionnaire) • Health care utilization in last 6 months (self-reported physician visits, ER visits, days hospitalized) 	<p>Burden of menopausal symptoms</p> <p>46.7% of women had ≥ 1 listed menopausal symptom, which included anxiety, decreased interest in sex, depression, forgetfulness, heart racing or pounding, hot flashes, insomnia/difficulty sleeping, joint stiffness, mood changes, night sweats, urine leakage, or vaginal dryness</p> <p>Health-related QOL</p> <p>Presence of menopausal symptoms was associated with significantly lower mental and physical health-related QOL vs women not experiencing menopausal symptoms ($P < 0.05$)</p> <p>Productivity and health care utilization</p> <ul style="list-style-type: none"> • Women with menopausal symptoms reported significantly higher presenteeism (17.7% vs 13.6%; $P < 0.05$) and overall work impairment (16.1% vs 12.3%; $P < 0.05$) than women without menopausal symptoms, but absenteeism was similar between groups (3.7% vs 3.4%; $P = 0.50$) • Women with menopausal symptoms had significantly higher impairment in daily activities (28.1% vs 23.3%; $P < 0.05$) and significantly more physician visits in past 6 months (2.1 vs 1.9; $P < 0.05$) vs women without menopausal symptoms, but number of ER visits (0.19 vs 0.17; $P = 0.05$) and hospitalizations (0.24 vs 0.22; $P = 0.40$) was similar <p>Burden of specific menopausal symptoms</p> <ul style="list-style-type: none"> • Depression, anxiety, heart racing, and forgetfulness were symptoms with strongest effects on health-related QOL and activity impairment • Joint stiffness was only symptom significantly associated with overall work impairment • Vaginal dryness, depression, and forgetfulness were significantly associated with increased physician visits, and night sweats, mood changes, and depression were significantly associated with increased ER visits

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
<p>NHWS – 2005: Cross-sectional Study of Depression, QOL, Work Productivity, Resource Use, and Costs Among Women Experiencing Menopause and Hot Flashes [69]</p> <p>US</p>	<p>Data obtained from 2005 NHWS, a self-administered internet-based questionnaire representative of US adult population, were used to evaluate the impact of depression on health-related QOL and productivity, and health care resource utilization and costs among women with menopausal symptoms and hot flashes</p>	<p>Females aged 40-64 years with no history of cancer or bipolar disorder and presence of menopausal symptoms and hot flashes (N = 3,632)</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Depression (yes vs no in last 12 months) • Health-related QOL (SF-8) • Work productivity (WPAI questionnaire) • Health care utilization in last 6 months (self-reported health care provider visits, ER visits, days hospitalized) 	<p>Adjusted health-related QOL, work productivity, and resource use</p> <p>Women with menopausal symptoms and depression had significantly worse health outcomes than women with menopausal symptoms without depression, these included lower mental and physical health-related QOL; greater levels of absenteeism, presenteeism, and activity impairment; and higher numbers of physician visits, ER visits, and days hospitalized (<i>P</i> <0.05 for all)</p> <p>Indirect and direct costs</p> <p>Indirect (\$7,650 vs \$4,584 per employed woman per year; <i>P</i> <0.0001) and direct costs (\$2,642 vs \$1,567 per woman per year; <i>P</i> <0.0001) were significantly higher for women experiencing depression than for those without depression</p>
<p>NHWS Analyses – 2010: Impact of Presence and Severity of VMS on Health Status, Productivity, and Health Care Resource Use and Costs [70]</p> <p>US</p>	<p>Data obtained from 2010 NHWS, a self-administered internet-based questionnaire representative of US adult population, were used to evaluate the impact of the presence and severity of VMS on health status, productivity, and health care resource use and costs</p>	<p>Females aged 40-75 years with no menstrual bleeding or spotting for ≥1 year (N = 3,267)</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Menopausal symptoms (MRS) • Work productivity (WPAI questionnaire) • Health status (EQ-5D) • Resource use during past 6 months (defined by menopause-related physician visits) 	<p>Work productivity loss</p> <ul style="list-style-type: none"> • Among employed women with VMS, increasing severity associated with increase in adjusted mean level of presenteeism (4.04% [mild] vs 14.46% [moderate] vs 24.28% [severe]; <i>P</i> <0.0001) and overall work impairment (4.33% [mild] vs 14.30% [moderate] vs 24.56% [severe]; <i>P</i> <0.0001) • In women with VMS regardless of employment, increasing VMS severity associated with increase in adjusted mean level of activity impairment (6.16% [mild] vs 17.06% [moderate] vs 31.66% [severe]; <i>P</i> <0.0001) <p>Health status</p> <p>Women experiencing severe and moderate VMS had significantly lower mean health status scores vs women with no symptoms (<i>P</i> <0.0001)</p> <p>Resource use</p> <p>Adjusted mean number of menopause symptom-related physician visits was significantly higher for women with severe, moderate, and mild VMS symptoms vs women with no symptoms (<i>P</i> <0.0001)</p> <p>Health outcomes stratified by years since FMP</p> <p>Effects of no VMS and mild VMS were similar for women <5 years or 5-10 years since FMP, but effect of moderate and severe VMS was more detrimental for women 5-10 years vs <5 years since FMP, including lower health status and higher overall work impairment and menopause-related physician visits</p> <p>Cost analyses</p>

Reference	Study design	Sample size/ Population	Treatments	Endpoints	Results
					Costs associated with observed presenteeism, overall work impairment, and menopause-related physician visits increased with severity of VMS
WHPI Burden of Illness Study [85] US	Cross-sectional, prospective study that collected data from nationally representative sample of women in the United States using the EXCEL Omnibus Survey to estimate prevalence of individual and coexisting conditions (pain, UI, MDD, osteoporosis risk, moderate/severe VMS, and VVA), their associated health status, and patterns of health-seeking behavior related to each condition	English- or Spanish-speaking women aged 40-64 years selected from both landline and cellular telephone random digit dialing samples (N = 3,058)	N/A	<ul style="list-style-type: none"> • Condition-specific symptom/risk screening instruments • Health status (EQ-5D) • Health-seeking behavior questions (discussion with doctor/clinician and prior treatment of the 6 conditions) 	<p>Health status</p> <ul style="list-style-type: none"> • Health status declined significantly with each added condition (pairwise $P < 0.01$) • Health status differed significantly between women with and without each of the 6 conditions ($P < 0.01$); except for osteoporosis risk, presence of any condition was associated with lower perceived health status vs absence of condition • Proportion reporting “unable or extreme problems” for each EQ-5D dimension increased with additional conditions • Proportion reporting no problems, some or moderate problems, or unable or extreme problems was significantly different in women with or without each condition ($P < 0.01$) <p>Health-seeking behavior</p> <ul style="list-style-type: none"> • For women who screened positive for a given condition, the percent who discussed it with her doctor ranged from 40.3% (VVA) to 89.7% (MDD), while those reporting treatment for the condition ranged from 13.1% (osteoporosis risk) to 69.2% (pain)

CE, conjugated estrogens; BZA, bazedoxifene; SMART, Selective estrogen Menopause And Response to Therapy; YSM, years since menopause; PBO, placebo; QOL, quality of life; MENQOL, Menopause-Specific Quality of Life; MOS, Medical Outcomes Study; MS-TSQ, Menopause Symptoms-Treatment Satisfaction Questionnaire; HT, hormone therapy; AE, adverse event; ER, emergency room; MEPS, Medical Expenditure Panel Survey; MRS, Menopausal Rating Scale; NHWS, National Health & Wellness Survey; WPAI, Work Productivity and Activity Impairment; VMS, vasomotor symptoms; FMP, final menstrual period; UI, urinary incontinence; MDD, major depressive disorder; VVA, vulvar/vaginal atrophy.

6.0 SUPPORTING INFORMATION

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