EXPERT OPINION

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# Emerging hormonal treatments for menopausal symptoms

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***Introduction:*** The majority of women experience bothersome symptoms post-menopause (e.g., hot flushes, vaginal symptoms). Estrogen receptor agonists remain the most effective options for ameliorating menopausal symptoms. However, use of hormonal therapies has declined in the wake of issues raised by the Women's Health Initiative trials. As a result, there is a need for new safe and effective alternatives to estrogen-progestogen hormone therapy.

***Areas covered:*** We review the efficacy and safety profile of hormonal menopausal therapies that are in Phase III clinical trials or recently approved. Investigational treatments discussed include two new vaginal estrogen products (TX-004HR, WC-3011); the first combination of estradiol and progesterone, and a novel combination of dehydroepiandrosterone and acolbifene. We also review a new selective estrogen receptor modulator (SERM), ospemifene, recently approved for treatment of dyspareunia related to menopause, and conjugated estrogens plus bazedoxifene, an estrogens/SERM combination, recently approved for moderate-to-severe vasomotor symptoms and prevention of osteoporosis.

***Expert opinion:*** New and emerging hormonal treatments for managing menopausal symptoms may have improved safety and efficacy profiles compared with traditional estrogen-progestogen therapy; however, long-term safety data will be needed.

**Keywords:** conjugated estrogens/bazedoxifene, dehydroepiandrosterone/acolbifene, estrogen receptors, hormone therapy, menopause, ospemifene, TX-001HR, TX-004HR, WC-3011

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## 1. Background

A majority of women experience menopausal symptoms of varying severity. The most common menopausal symptoms are vasomotor symptoms (VMS) consisting of hot flushes and night sweats. VMS affect ~ 75 – 90% of women [1,2], typically during perimenopause and early postmenopause [3,4]. Nearly 50% of postmenopausal women experience vulvar-vaginal atrophy (VVA), which can lead to bothersome symptoms of vaginal dryness, itching, irritation, infection, discharge or bleeding, as well as dyspareunia and urinary symptoms (frequency, urgency, incontinence) [5]. Furthermore, women experience a rapid acceleration of bone loss following menopause, which puts them at increased risk for osteoporosis and fracture [6].

Not all menopausal symptoms are bothersome or require medical attention, but for many women, they do. According to a meta-analysis of six trials, > 50% of menopausal women experience VMS symptoms, they considered bothersome or that were moderate to severe, with peak incidence occurring at 1 to 2 years postmenopause [3]. Similarly, a more recent survey conducted in Estonia reported that 45.7% of women aged 50 – 59 years had bothersome VMS symptoms, accounting for 67.3% of those with any VMS [7]. VMS can have an adverse effect on sleep, mood, cognition, social interactions, occupational productivity and other quality-of-life issues [8]. VVA can have a negative impact on sexuality, self-esteem and intimate partner relationships [9].

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As menopausal symptoms and postmenopausal osteoporosis are clearly related to declining levels of estrogens postmenopause, estrogen-containing hormone therapeutics targeting estrogen receptors (ER) have been found to be highly effective [5,6,8,10,11]. However, dramatic reductions in hormone therapy (HT) use have taken place over the past 12 years since safety concerns were raised by the Women's Health Initiative (WHI) and other trials (described below). Although HT use varies widely by country, there was a 50 – 77% decrease in HT use in Europe from 2002 to 2010, such that by 2010, except in Finland, < 10% of European women aged 45 – 69 were using HT [12]. Similarly, in the US, whereas 22% of women aged 40 years or older were using HT in 1999 – 2000, < 5% were using HT in 2009 – 2010 [13]. Thus, there is a need for safe and effective new treatment options for management of bothersome, moderate-to-severe menopausal symptoms.

## 2. Medical need

An ideal menopausal therapy would reduce the frequency and severity of hot flushes, treat VVA, prevent/treat osteoporosis and have favorable effects on cardiovascular risk factors (e.g., lipids, blood pressure, body weight), without stimulating the endometrium or breast, inducing breast pain/tenderness or vaginal bleeding or increasing the risks of venous thromboembolism (VTE) or stroke [14]. To date, no menopausal therapy has been able to achieve all these objectives.

## 3. Existing treatments

HT is the most effective option and remains the standard of care for ameliorating hot flushes; it also reduces VVA and postmenopausal osteoporotic fractures [11]. However, in the randomized Women's Health Initiative (WHI) trial, conjugated estrogens/medroxyprogesterone acetate (CE/MPA) was associated with an increased risk of breast cancer (hazard ratio [HR] 1.25; 95% CI, 1.07 – 1.46) and related mortality (HR 1.96; 95% CI, 1.00 – 4.04) in women with a uterus [15,16]. In contrast, the randomized WHI trial of CE alone in hysterectomized women, there was no increase in breast cancer risk; in fact, CE was associated with a significant protective effect during cumulative follow-up including postintervention (HR 0.79; 95% CI, 0.65–0.97) [17,18]. A progestin must be given with estrogen(s) in nonhysterectomized women to prevent estrogen's stimulation of the endometrium and reduce the risk of endometrial cancer [11]. In the randomized WHI trials, both CE and CE/MPA were associated with statistically significant increased risks of stroke (CE: HR 1.35; 95% CI, 1.07 – 1.70; CE/MPA: HR 1.37; 95% CI, 1.07 – 1.76) and deep vein thrombosis (CE: HR 1.48; 95% CI, 1.06 – 2.07; CE/MPA: HR 1.87; 95% CI, 1.37 – 2.54) [18]. Increased risks of pulmonary embolism (CE: HR 1.35; 95% CI, 1.07 – 1.70; CE/MPA: 1.98; 95% CI, 1.36 – 2.87) and (in women aged 65 years or older) probable dementia (CE: HR 1.47; 95% CI, 0.85 – 2.52; CE/MPA: HR 2.01; 95% CI, 1.19 – 3.42) were also observed but were statistically significant only in the CE/MPA group [18]. US labeling for all estrogen- and estrogen/progestin-containing HT products contains a black box warning citing these risks and referencing the WHI trials [19,20].

Numerous analyses and reanalyses of WHI data followed the original publications, with results and interpretations shifting a bit over time. Recent subset analyses from the WHI trials suggest some risks are influenced by the woman's age or duration of time since menopause at the start of HT. Among hysterectomized women using CE alone, risk of all-cause mortality, myocardial infarction and global index (a composite of stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture and death risk) were all lowest in the youngest age group (50 – 59 years), and risk increased significantly with increasing age (p for trend by age group = 0.02 for myocardial infarction and global index; p = 0.04 for mortality) [18]. Those outcomes did not significantly differ by age in the CE/MPA trial [18]; however, women < 10 years since menopause had a lower risk of coronary heart disease (CHD) (HR 0.88; 95% CI, 0.54 – 1.43) compared with women 10 – 19 years postmenopause (HR 1.23; 95% CI, 0.85 – 1.77) or > 20 years postmenopause (HR 1.66; 95% CI, 1.14 – 2.41) (p = 0.05 for the trend) [21]. Risk of breast cancer was greater among women who began CE/MPA within 5 years of menopause (HR 1.41; 95% CI, 1.14 – 1.74) compared with those who started > 5 years after menopause (HR 1.15; 95% CI, 0.96 – 1.37), but this difference was not statistically significant (p = 0.08) [16]. In hysterectomized women who received CE alone, there was no statistically significant difference (p = 0.68) in breast cancer risk by time since menopause [17].

Selective estrogen receptor modulators (SERMS), such as raloxifene, bazedoxifene (BZA) and tamoxifen, are effective for osteoporosis and/or breast cancer prevention and treatment but increase the risk of VMS and therefore cannot be used to treat menopausal symptoms [22-28]. Some, particularly tamoxifen, also have estrogenic effects on the endometrium, whereas others have a neutral effect (raloxifene) or possibly even an antagonistic effect (BZA) [23-27,29,30].

Paroxetine is the first nonhormonal treatment approved for moderate-to-severe VMS of menopause [31]. Paroxetine is a selective serotonin reuptake inhibitor. Its mechanism in treating VMS is unknown [31] but two serotonin receptors (5-$HT_{1a}$ and 5-$HT_{2a}$) are known to contribute to thermoregulation [32].

Paroxetine 7.5 mg/day for 12 weeks (n = 614) or 24 weeks (n = 570) was evaluated in two randomized, placebo-controlled Phase III studies of postmenopausal women who were experiencing a mean of at least seven to eight moderate-to-severe hot flushes per day or 50 – 60 per week at screening [32]. Paroxetine modestly but significantly reduced the frequency of VMS compared with placebo; mean weekly reductions at week 12 were –43.5 versus –37.3 (p = 0.0090) in the first study and –37.2 versus –27.6 (p = 0.0001) in the

**Table 1. Wholesale amounts for hormone therapy products: 2009 and 2010 [37].**

| | 2009 | 2010 |
|---|---|---|
| Estrogens | $1.542 billion | $1.576 billion |
| Progestogens | $229 million | $243 million |
| Estrogen-progestogen combinations | $394 million | $399 million |

second trial. Reductions in mean weekly hot flush severity at week 12 were significant in the 24-week study (–0.12 vs –0.07; p = 0.0114) but not the 12-week study (–0.10 vs –0.09; p = 0.2893). Paroxetine provides a potentially useful alternative for women who do not want to take or are not eligible for hormonal treatments; however, given the small magnitude of effect seen in this study, paroxetine is not likely to be as effective as HT in relieving VMS.

At the approved dose of paroxetine (7.5 mg/day), which is lower than that used to treat psychiatric conditions, rates of serious AEs are similar to placebo. However, the labeling still carries warnings concerning suicidality and other risks associated with selective serotonin reuptake inhibitors [31]. At the approved dose, paroxetine did not increase body weight or sexual dysfunction [33]. Given that paroxetine, which is a strong CYP2D6 inhibitor, reduces the efficacy of tamoxifen, it is not a good treatment option for many breast cancer patients [31].

## 4. Market review

Both randomized WHI trials of HT were terminated early [15,34,35]. In 2002, the WHI study of CE/MPA in nonhysterectomized women was terminated by its Data Safety and Monitoring Board (DSMB), which determined that benefits were outweighed by an increased risk of invasive breast cancer, as well as CHD, stroke and pulmonary embolism (as described in Section 3 above) [15,35]. In 2004, the National Institutes of Health terminated the WHI study of CE alone in hysterectomized women, despite the DSMB's assessment that none of the predefined stopping boundaries had been crossed [34]. According to the National Institutes of Health, CE had not affected CHD risk (positively or negatively) but had increased the risk of stroke [34]. Around the same time, results began to emerge from the Million Women Study, an observational UK-population-based study, which also reported an association between HT (particularly progestogen-estrogen combination therapies) and an increased risk of breast cancer [36]. Results of these studies, especially the WHI, were widely published in the medical literature and lay press, and were followed by a dramatic and steady decline in HT use [12,13].

Despite the decline in the number of HT prescriptions, there are continued modest increases in wholesale expenditures for HT in recent years (**Table 1**) [37]. According to figures from the North American Menopause Society, using data from IMS Health, Premarin (CEs) and estradiol each accounted for about one quarter of market share for estrogens; Prometrium (progesterone) and MPA each accounted for > 40% of the market share for progestogens; and Prempro and Prempro low dose combined accounted for nearly 55% of the market share for estrogen-progestogen combination products in 2010 (**Figure 1**) [37].

With the decline in HT use following the WHI and the Million Woman Study, there is a need for new safe and effective alternatives to estrogen-progestogen HT for bothersome menopausal symptoms. Physicians report that their patients frequently ask about alternatives to traditional oral HT regimens [38]. As rates of overall HT use have fallen, prescriptions for vaginal products containing one or more estrogens, which are thought to have fewer systemic effects, have steadily risen 89% from 2001 to 2010, and the popularity of compounded menopausal hormones has increased (despite a lack of efficacy and safety data), attesting to an ongoing demand for products that can provide relief from menopausal symptoms [37,39].

## 5. Current research goals

Research has focused on the development of menopausal therapies that come closer to the ideal therapy described earlier. A primary goal has been to design a treatment that preserves the beneficial effects of estrogens on VMS, VVA and bone, but with improved breast and endometrial safety profiles. The greatest need is for alternatives to combination estrogen-progestogen therapy for nonhysterectomized women because the biggest risks appear to be associated with progestogen-containing regimens.

One regulatory consideration for all estrogen- or estrogen/progestin-containing therapies in development is the US FDA requirement for a black box warning in the product labeling that contains a description of the risks observed in the WHI trials [19,20]. Because early preclinical findings and intermediate risk markers did not predict many of the adverse outcomes observed in the large, randomized WHI trials, for a new hormone-based agent to have the black box removed from its label, a safety study of sufficient size and duration to determine impact on potentially hormone-mediated chronic disease risk would be needed.

## 6. Scientific rationale

Estrogens and SERMs interact with and activate ERs. There are two ER types – $\alpha$ and $\beta$ [10]. The relative expression of ER-$\alpha$ and -$\beta$ varies in different tissues [10]. Individual estrogens and SERMs each induce a unique ER conformation [10,40] and also differ with regard to recruitment of coactivator or corepressor proteins [10,40]. As a result, estrogens, SERMs and their combinations vary with regard to effects on gene regulation [40-43]. In other words, each estrogen and SERM has a unique profile with regard to its ER activity in different tissues. Thus, it may be possible to come closer to the ideal by

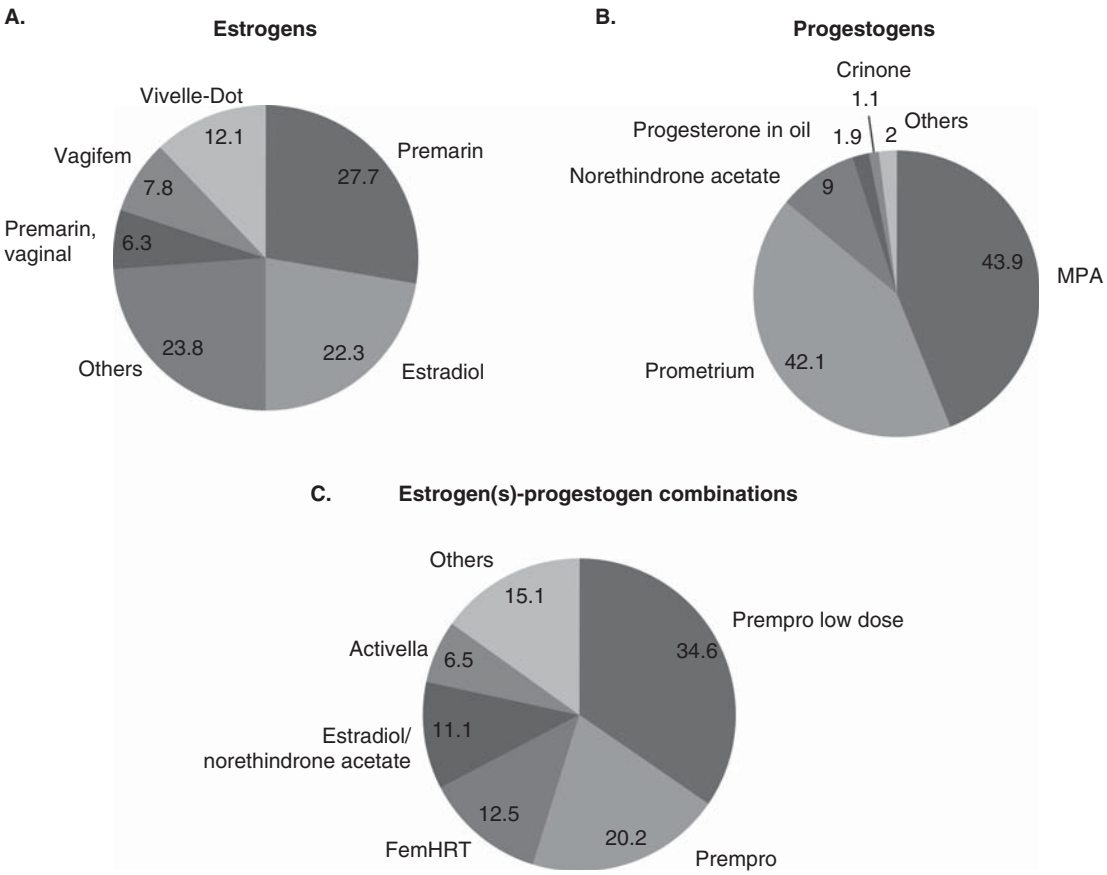


**Figure 1. Market share in 2010 for individual estrogens (A), progestogens (B) and combination products (C) [37].**
Adapted from [37] with permission from the North American Menopause Society.
MPA: Medroxyprogesterone acetate.

selecting or designing hormonal therapies with improved profiles of ER activity.

New menopausal therapies that obviate the need for a progestogen in women with a uterus are also desirable. Progesterone has various proliferative effects in the breast, independent of estrogens and the ER [44-48]. For example, progesterone receptor signaling activates pathways that may contribute to breast carcinogenesis (e.g., RANKL, cyclin D1, WNT4) and angiogenesis (VEGF) and other progesterone receptor signaling pathways (Stat3, c-Myc) may also downregulate the tumor suppressor miR-16 [45-47].

## 7. Competitive environment

Six new therapies for treatment of menopausal symptoms are in late-stage development or recently approved (**Table 2**). Therapies currently in Phase III trials include two new formulations of vaginal estrogen therapies for treatment of VVA, a new oral combination of estradiol and micronized progesterone, and a combination of dehydroepiandrosterone (DHEA) and the ER antagonist acolbifene. A new SERM, ospemifene, was recently approved in the US as an oral treatment for moderate-to-severe dyspareunia, a symptom of VVA, due to menopause [49], and is currently under review in the European Union for treatment of VVA in postmenopausal women [50]. In addition, CE 0.45 mg/BZA 20 mg – the first tissue selective estrogen complex (TSEC) consisting of a combination of estrogen(s) and an SERM – was approved by the US FDA in 2013 for treatment of moderate–to-severe VMS associated with menopause and prevention of postmenopausal osteoporosis [51]. CE/BZA is currently under review in the European Union for treatment of menopausal symptoms (VMS and VVA) and prevention of osteoporosis.

### 7.1 Investigational vaginal estrogen therapies for VVA

Vaginal estrogen products in the form of creams, pessaries, tablets and rings are effective treatments of VVA and have fewer systemic effects than oral estrogens, although endometrial stimulation remains a potential concern [52]. The 2013 North American Menopause Society (NAMS) Position Statement on VVA recommends low-dose vaginal estrogen therapy for women whose VVA does not respond satisfactorily to

**Table 2. Competitive environment.**

| Compound | Company | Chemical name | Indication | Stage of development | Mechanism of action |
|---|---|---|---|---|---|
| TX-004HR (Estradiol VagiCap vaginal suppository) | TherapeuticsMD | (17β)-Estra-1,3,5(10)-triene-3,17-diol | VVA | Phase IIb/III was initiated Q3 2014 | Vaginal ER agonist |
| WC-3011 (estradiol cream/gel) | Actavis (formerly Warner Chilcott) | Estra-1,3,5(10)-triene-3,17-diol, (17β)- | Postmenopausal vaginal dryness due to VVA | Phase III | Vaginal ER agonist |
| TX-001HR (17-β estradiol/ progesterone) | TherapeuticsMD | Estra-1,3,5(10)-triene-3,17-diol (17β)- [CAS] + Pregn-4-ene-3,20-dione- | Menopausal symptoms | Phase III | Oral fixed dose combination of ER agonist+progesterone receptor agonist |
| Prasterone (dehydroepiandrosterone [DHEA])/acolbifene | Endoceutics | (3β)-17-Oxoandrost-5-en-3-yl heptanoate + (2S)-3-(4-Hydroxyphenyl)-4-methyl-2-{4-[2-(1-piperidinyl)ethoxy]phenyl}-2H-chromen-7-ol | Symptoms of menopause including bone loss, muscle loss, type 2 diabetes, fat accumulation, osteoporosis, hot flushes, memory loss, cognition loss, and Alzheimer's disease | Phase III (Canada) | Oral fixed dose combination of protein synthesis stimulant + SERM |
| Ospemifene | Shionogi | Z-2-[4-(4-chloro-1,2-diphenylbut-1-enyl) phenoxy]ethanol | Moderate/severe dyspareunia, a symptom of VVA due to menopause | Approved in the US in 2013; EU review pending | Oral SERM |
| Conjugated estrogens/bazedoxifene | Pfizer | Sodium (13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,-17-decahydro-6H-cyclopenta[a]phenanthren-3-yl sulphate + 1-(p-(2-(Hexahydro-1H-azepin-1-yl)ethoxy)benzyl)-2-(p-hydroxyphenyl)-3-methylindol-5-ol monoacetate (salt) | US: moderate/severe VMS and prevention of postmenopausal osteoporosis. EU (pending): symptoms of estrogen deficiency (VMS, VVA) and prevention of postmenopausal osteoporosis | Approved in the US in 2013; EU review pending | Oral fixed-dose combination of ER agonists + SERM |

ER: Estrogen receptor; EU: European Union; SERM: Selective estrogen receptor modulator; VMS: Vasomotor symptoms; VVA: Vulvar-vaginal atrophy.

nonhormonal interventions (e.g., lubricants, moisturizers, regular sexual activity) and notes that it is more effective and has a lower risk profile than oral HT for women whose only menopausal symptoms are vaginal [53]. Two new vaginal estrogen products for treatment of VVA are in Phase III development: TX-004 (estradiol VagiCap vaginal suppository) and WC-3011 (estradiol cream/gel) [54-59].

TX-004HR is tear-shaped estradiol softgel capsule that may be inserted manually (without an applicator) into the vagina where it dissolves quickly without producing a burning sensation [54]. Repeated applications of TX-004HR over 28 days were found to be nonirritating in rabbits [60]. Two single-dose crossover pharmacokinetic studies, reported only in press releases to date, showed less systemic absorption and lower maximal concentration and overall systemic exposure with TX-004HR (10 or 25 μg) than with Vagifem vaginal estradiol tablets (10 or 25 μg) [61,62].

Once daily TX-004HR administered for 2 weeks was evaluated in a Phase II, placebo-controlled pilot study of postmenopausal women with VVA (n = 48) [54]. According to the sponsor, TX-004HR was associated with significant decreases in parabasal cells ($p < 0.0001$) and increases in superficial cells ($p = 0.0002$) [maturation index 44.48 vs 7.08 with placebo], as well as decreases in vaginal pH (–0.92 vs –0.40; $p = 0.0002$). Furthermore, TX-004HR reduced atrophic effects on epithelial integrity and vaginal secretions [54].

The sponsor has indicated that a 12-week Phase IIB/III trial will start in the third quarter of 2014. This study will randomly assign women to TX-004HR at doses of 4, 10, or 25 μg (n = 150 – 200 subjects each) or placebo (n = 100). End points will include superficial and parabasal cell changes, pH, and VVA-related symptoms of dyspareunia and vaginal dryness [54].

Several Phase III studies of WC-3011 estradiol cream/gel are listed as having recently been completed on clinicaltrials.gov (**Table 3**); however, results have not yet been reported [55-59].

**Table 3. Phase III trials of WC-3011 estradiol gel for VVA.**

| Clinicaltrials.gov identifier | Target enrollment | Interventions | Description | Primary end points | Status |
|---|---|---|---|---|---|
| NCT01400776 (VENUS Study) [55] | 722 healthy postmenopausal women with moderate-to-severe vaginal dryness | 4 arms: WC-3011 once daily for 2 weeks, then either twice weekly or thrice weekly for 10 weeks or placebo gel once daily for 2 weeks, then either twice weekly or thrice weekly for 10 weeks | Randomized, double-blind, vehicle-controlled trial | Change in vaginal cytology and vaginal pH and change in self-assessed vaginal dryness from baseline to week 12 | Completed |
| NCT01816139 [59] | 576 healthy postmenopausal women with moderate-to-severe vaginal dryness | WC-3011 (0.15 mg estradiol/0.5 g vehicle) or vehicle (0.5 g) daily for 14 days then twice weekly for 10 weeks | Randomized, double-blind, vehicle-controlled trial | Change in self-assessed intensity of vaginal dryness, and change in vaginal pH and percentage of vaginal superficial cells from baseline to week 12 | Completed |
| NCT01845649 [57] | 550 healthy postmenopausal women who are sexually active with self-identified moderate-to-severe dyspareunia and most bothersome symptom of VVA | WC-3011 (0.03 mg estradiol/g) or vehicle daily for 14 days, then thrice weekly for 10 weeks | Randomized, double-blind, vehicle-controlled trial | Change in self-assessed dyspareunia, and in maturation index, and vaginal pH from baseline to week 12 | Completed |
| NCT01455597 [56,59] (VENUS Study Extension) | 309 nonhysterectomized, healthy postmenopausal women with VVA | WC-3011 (0.017 mg estradiol/g) thrice weekly for 40 weeks | Open-label extension of VENUS to evaluate long-term safety and efficacy | Number of subjects without endometrial hyperplasia or worse at week 40 | Completed |

VVA: Vulvar-vaginal atrophy.

### 7.2 A new combination estrogen/progesterone therapy

TX-001HR is the first product being developed for FDA approval to combine 17-β estradiol and progesterone into a single oral capsule. The individual components have long been available, but combined estradiol/micronized progesterone has been available only through pharmacy compounding. According to the US FDA, although some pharmacists are well-trained and capable of preparing compounded medications correctly, pharmacy-compounded drugs may be associated with added safety risks or potentially reduced efficacy if poor-quality compounding practices are employed [63]. According to the American College of Obstetrics and Gynecology, compounded estradiol/micronized progesterone is not supported by evidence of benefit in treating VMS [64]. TX-001HR contains micronized progesterone and 17-β estradiol in a solubilized gelatin capsule that does not contain peanut oil (a common allergen, present in other commercial progesterone products) [54,65,66].

Estradiol and micronized progesterone are often referred to as 'bioidentical' hormones [39]. However, the US FDA does not recognize the term 'bioidentical' and points out that definitions of this term by major medical societies are inconsistent [63]. The FDA has sent letters to compounding pharmacies warning them that claims that 'bioidentical hormone replacement therapy' drugs are more 'natural', safer or more effective than FDA-approved drugs are false/misleading claims not backed by credible scientific evidence [63].

In a single-dose, crossover trial in healthy postmenopausal women aged 40 to 65 years (n = 66), TX-001HR exhibited bioavailability comparable to that of coadministered Prometrium (progesterone) and Estrace (17-β estradiol) with similar extent of absorption, but more rapid estradiol absorption [66]. Compared with Estrace and Prometrium given concurrently, the fixed combination of TX-001HR was associated with a slightly faster rate of estradiol absorption ($T_{max}$ 9.0 vs 10.0 min, respectively) [66].

A Phase III, randomized, double-blind, trial (REPLENISH, NCT01942668) is ongoing [54,67]. REPLENISH is enrolling approximately 1750 healthy postmenopausal women with a uterus who had serum estradiol ≤ 50 pg/ml at screening and who were seeking relief from VMS.

Participants were randomly assigned to four active-treatment groups (not specified; n = 400 in each) or placebo (n = 150). End points include VMS frequency and severity at weeks 4 and 12, and the incidence of endometrial hyperplasia at 12 months. REPLENISH also includes a 12-week VMS substudy, which is enrolling women with a minimum of seven moderate-to-severe hot flushes per day or 50 per week.

### 7.3 DHEA + ER antagonist

A combination of oral prasterone (DHEA) and acolbifene is being investigated for treatment of menopausal symptoms [68]. and possibly for prevention of osteoporosis, breast cancer and Alzheimer's disease [69]. DHEA is converted intracellularly into estrogens and/or androgens in peripheral target tissues and serves as a significant source of estrogens postmenopause [70]. Endogenous DHEA declines with age but to a widely varying extent [70]. Acolbifene is a SERM reported to have ER antagonist activity in the breast and uterus but estrogen agonist effects on bone [71].

The rationale for combining DHEA with acolbifene is to potentially derive a product that combines the benefits of both components. For example, benefits with regard to prevention of osteoporosis may be additive given DHEA's anabolic effects (i.e., stimulation of bone formation) and acolbifene's ability to reduce bone loss [70] (Labrie, written communication May 14, 2014). In preclinical studies, topically applied DHEA combined with oral acolbifene increased the compactness of collagen fibers in the lamina propria, vaginal muscle thickness, mucification, and the density of nerve fibers in the vaginas of ovariectomized rats [72,73].

A Phase III multi-centre Canadian trial of DHEA/acolbifene in postmenopausal women with moderate-to-severe hot flushes (n = 238) has been completed (NCT01452373) [68] but data have not yet been reported. The primary end points of this study were change from baseline to week 12 in frequency and severity of moderate-to-severe hot flushes. Secondary end points consisted of change from baseline to week 12 in VVA (i.e., superficial/parabasal cell counts, pH, atrophy symptoms), as well as sexual function and quality of life (based on questionnaires). Safety/tolerability is also a secondary end point.

### 7.4 A new SERM

Ospemifene was approved by the US FDA in 2013 as an oral treatment for moderate-to-severe dyspareunia associated with VVA and menopause [49]. The approved dose is 60 mg once daily, taken with food [49].

A Phase III, 12-week, randomized, double-blind, placebo-controlled trial (NCT00276094) of ospemifene 30 or 60 mg was conducted in postmenopausal women (n = 826) with VVA, defined as ≤ 5% superficial cells, pH > 5.0, and the presence of ≥ 1 moderate-to-severe VVA symptom [74]. Ospemifene 30 and 60 mg, compared with placebo, both significantly ($p < 0.001$) increased the percentage of superficial cells by 7.8 and 10.8%, versus 2.2%, respectively, and decreased the percentage of parabasal cells by 21.9 and 30.1%, versus 3.98%, respectively [74]. Vaginal pH decreased by 0.67 in women treated with the 30 mg dose of ospemifene and by 1.01 with the 60 mg dose compared with 0.10 with placebo [74]. Symptom severity was assessed via patient self-report using a Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The ospemifene 60-mg dose significantly decreased dyspareunia such that the severity score was decreased by 1.19 versus 0.89 with placebo ($p = 0.023$) in women who reported that dyspareunia was their most bothersome VVA symptom. Both the 30 and 60 mg doses significantly ($p < 0.05$) decreased vaginal dryness compared with placebo among women for whom dryness was the most bothersome VVA symptom (score reductions of 1.22, 1.26, and 0.84, respectively) [74].

Similar results were reported in another Phase III, 12-week study (NCT00729469) of ospemifene 60 mg in postmenopausal women with moderate-to-severe dyspareunia (n = 605) [75]. At the end of the 12-week treatment period, the ospemifene group experienced a 40.2% reduction in parabasal cells, a 12.3% increase in superficial cells, a 0.94 reduction in pH, and a 1.5 point reduction in severity of dyspareunia (using the same Likert scale defined above), whereas the placebo group had no reduction in parabasal cells, a 1.7% increase in superficial cells, a 0.07 reduction in pH, and a −1.2 point change in severity score ($p \leq 0.0001$ for all comparisons) [75]. In both 12-week studies, hot flushes were the most common adverse event (AE) (6.6 to 9.6% vs 3.4 to 3.6% with placebo) [74,75].

Ospemifene 60 mg also was evaluated in a 12-month, randomized, double-blind, placebo-controlled safety and efficacy study (NCT00566982) in postmenopausal women with VVA, defined as ≤ 5% superficial cells and pH > 5 (n = 426) [76]. As in the 12-week studies, ospemifene significantly ($p < 0.0001$) increased superficial cells (5% vs 0), and decreased parabasal cells (−40% vs 0) and vaginal pH (−1.21 vs −0.16) compared with placebo. Hot flushes were again the most common AE (12.6 vs 6.5%). Bleeding/spotting and breast pain were reported in 1.4 and 1.1% respectively, compared with none of the controls. There were two cerebrovascular accidents and one deep vein thrombosis in the ospemifene group.

Ospemifene has some ER agonistic effects on the endometrium; therefore, proper consideration should be given to its use in women with a uterus [49]. In all three of the studies, including a 40-week extension of the first 12-week study, there was an increase in endometrial thickness (evaluated by transvaginal ultrasound) with ospemifene (0.40 – 1.14 mm) relative to placebo (−0.04 – 0.17) [74-77]. Endometrial histology assessments showed active endometrial proliferation in 1.0 – 1.6% of the ospemifene-treated women and none of the controls [75-77].

### 7.5 Tissue selective estrogen complex

The rationale for combining estrogens with a SERM is to retain beneficial effects of estrogens on VMS, VVA, and

**Table 4. Design of Phase III CE/BZA SMART trials.**

| | SMART-1 (n = 3397) [82-86] | SMART-2 (n = 318) [87,88] | SMART-3 (n = 652) [89,90] | SMART-4 (n = 1061) [91] | SMART-5 (n = 1843) [92-94] |
|---|---|---|---|---|---|
| Clinicaltrials.gov study ID number | NCT00675688 | NCT00234819 | NCT00238732 | NCT00242710 | NCT00808132 |
| Study population | Generally healthy postmenopausal women aged 40 – 75 y with a uterus, BMI ≤ 32.2 kg/m$^2$ | Postmenopausal women aged 40 – 65 y with a uterus and ≥ 7 moderate-to-severe hot flushes daily or 50/week at screening, BMI ≤ 34.0 kg/m$^2$ | Postmenopausal women aged 40 – 65 y with a uterus and moderate-to-severe VVA, BMI ≤ 34.0 kg/m$^2$ | Generally healthy postmenopausal women aged 40 – 65 y with a uterus, BMI ≤ 34.0 kg/m$^2$ | Postmenopausal women aged 40 – 65 y with a uterus who were seeking treatment for menopausal symptoms, BMI ≤ 34.0 kg/m$^2$ |
| Study duration | 2 y | 12 weeks | 12 weeks | 1 y + 1 y extension | 1 y |
| Treatments (once daily oral dose), mg | CE 0.45/BZA 10<br>CE0.45/BZA 20<br>CE 0.45/BZA 40<br>CE 0.625/BZA 10<br>CE 0.625/BZA 20<br>CE 0.625 BZA<br>Raloxifene 60<br>PBO | CE 0.45/BZA 20<br>CE 0.625/BZA 20<br>PBO | CE 0.45/BZA 20<br>CE 0.625/BZA 20<br>BZA 20<br>PBO | CE 0.45/BZA 20<br>CE 0.625/BZA 20<br>CE 0.45/MPA 1.5<br>PBO | CE 0.45/BZA 20<br>CE 0.625/BZA 20<br>BZA 20<br>CE 0.45/MPA 1.5<br>PBO |
| Primary end points | Incidence of endometrial hyperplasia | Frequency/severity of hot flushes | Vaginal superficial cells, parabasal cells, pH, severity of most bothersome VVA symptom | Incidence of endometrial hyperplasia, change in lumbar spine BMD | Incidence of endometrial hyperplasia, per cent change in lumbar spine BMD |
| Secondary end points | Lumbar spine and total hip BMD, serum BTM, metabolic parameters, frequency/severity of hot flushes, VVA measures, uterine bleeding, sleep, MENQOL, breast density | Hot flush responders, breast pain, sleep, MENQOL, satisfaction with treatment | Vaginal intermediate cells, individual VVA symptoms, sexual function, satisfaction with treatment, MENQOL | Uterine bleeding/spotting, breast pain, change in total hip BMD, rates of amenorrhea | Hip BMD, serum BTM, cumulative amenorrhea, breast tenderness, breast density, sleep, MENQOL |
| Substudy populations | Osteoporosis Substudy 1: > 5 y postmenopausal, BMD of -1 to -2.5, ≥ 1 additional risk factor<br>Osteoporosis Substudy 2: 1–5 y postmenopause + ≥ 1 osteoporosis risk factor<br>Breast density: Participants who completed 24 mo treatment and all evaluations in core study with ≥ 80% compliance + evaluable mammograms at baseline and mo 24 | N/A | N/A | Osteoporosis: ≤ 5 y postmenopausal, evaluable lumbar spine and hip BMD scans at screening, no history or presence of osteoporosis or fragility fractures, lumbar spine/total hip T score ≥ -2.5 | Osteoporosis: ≤ 5 y postmenopausal, evaluable lumbar spine and hip BMD scans at screening, no history or presence of osteoporosis or fragility fractures, lumbar spine/total hip T score ≥ -2.5<br>Sleep/HRQoL: participants bothered by hot flushes/ night sweats and sleep disturbances<br>Breast density: technically acceptable mammogram at screening |

n: number of subjects randomized in core study who received at least 1 dose of study medication.

BMD: Bone mineral density; BMI: Body mass index; BTM: Bone turnover markers; BZA: Bazedoxifene; CE: Conjugated estrogens; HRQoL: Health-related quality of life; MENQOL: Menopause-specific quality of life; N/A: Not applicable; MPA: Medroxyprogesterone acetate; PBO: Placebo; SMART: Selective estrogens, Menopause, and Response to Therapy; VVA: Vulvar-vaginal atrophy; y: Years.

bone while incorporating the anti-estrogenic effects of the SERM on the breast and endometrium to improve the overall safety profile [14,78]. It was recently demonstrated that CE and BZA can form ER heteroligand dimer complexes resulting in cooperative gene regulation [79]. Furthermore, BZA has been found to degrade the ER in the endometrium and breast, suggesting it acts more like the pure antiestrogen fulvestrant than like other SERMs in these tissues [42,43,80,81]. BZA's antiestrogenic effects in endometrial tissue eliminate the need to include a progestin when combined with estrogens in women with a uterus.

Five Phase III, randomized, double-blind Selective estrogens, Menopause, And Response to Therapy (SMART) trials established the efficacy and safety of CE/BZA use for up to 2 years [82-94]. The design of the SMART trials is summarized in **Table 4**. CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg effectively reduced the frequency and severity of VMS [83,87]. For example, in SMART-2, women with moderate-to-severe hot flushes who received CE 0.45 mg/BZA 20 mg or CE 0.625 mg/BZA 20 mg had a 74 or 80%, respectively, reduction in mean daily number of hot flushes, compared with a 51% reduction in the placebo group [87]. In that study, average daily hot flush severity was calculated as the sum of mild (1 point), moderate (2 points) and severe (3 points) hot flushes divided by the total number of hot flushes that day. SMART-2 participants taking CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg showed a reduction from baseline in average daily hot flush severity score at week 12 that was statistically significant compared with placebo (–0.87 and –1.21 vs –0.26, respectively; both $p < 0.001$) [87].

SMART-2 and SMART-5 demonstrated that CE/BZA improves sleep parameters and menopause-related quality of life [88,93]. A SMART-5 substudy (n = 459) evaluated sleep and health-related quality of life using the Medical Outcomes Study sleep scale and Menopause-Specific Quality of Life (MENQOL) scale. Twelve weeks of CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg significantly improved time to fall asleep (–16.2 and –16.0, respectively, vs –8.6 with placebo; $p < 0.05$ for both), as well as sleep disturbance (–17.4 and –18.6 vs –12.0; $p < 0.05$ and $p < 0.001$, respectively) [93]. Total MENQOL score was significantly improved with CE 0.45 mg/BZA 20 mg (–1.42) and CE 0.625 mg/BZA 20 mg (–1.60) compared with placebo (–0.87; both $p < 0.001$), largely driven by improvements in vasomotor function domain score (–2.79 and –2.79 vs –1.14; both $p < 0.001$) [93].

CE/BZA reduced VVA in the SMART-1 and SMART-3 trials [83,89]. SMART-3 enrolled women with VVA (≤ 5% superficial cells, vaginal pH > 5, and endorsement of at least 1 bothersome, moderate-to-severe symptom of VVA) [89]. In nonparametric analyses, both CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg produced significantly greater increases in percentage of superficial cells ($p < 0.01$) (and decreases in parabasal cells ($p \leq 0.001$) compared with placebo.) At week 12, mean vaginal pH was significantly ($p < 0.001$) lower in the CE 0.625 mg/BZA 20 mg group compared with placebo, and CE 0.625 mg/BZA 20 mg also significantly ($p < 0.048$) reduced the most bothersome VVA symptoms. Both doses improved ease of lubrication [90].

The SMART trials demonstrated that CE/BZA increases bone mineral density (BMD) [85,91,94]. For example, in SMART-1, adjusted annual per cent change in lumbar spine BMD was a mean of 0.94 with CE 0.45 mg/BZA 20 mg, 1.04 with CE 0.625 mg/BZA 20 mg and –1.08 with placebo in women who were > 5 years postmenopause, had a baseline lumbar spine or hip BMD of –1 to –2.5, and who had ≥ 1 other osteoporosis risk factor (Osteoporosis Substudy 1) [85]. Adjusted annual per cent change in lumbar spine BMD was a mean of 1.01, 0.55 and –1.41 in those treatment arms, respectively, in women 1 – 2 years postmenopause who had at least 1 osteoporosis risk factor (Osteoporosis Substudy 2) [85]. In both substudies, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg were also associated with significant increases in total hip, femoral neck, femoral intertrochanteric and trochanteric region BMD [85]. In Substudy 2, both CE/BZA doses produced significantly ($p < 0.001$) greater reductions in bone turnover markers (osteocalcin and C-telopeptide) compared with placebo.

CE/BZA is generally well tolerated. Among women treated with CE/BZA in the SMART studies, rates of ischemic stroke, cardiovascular events and VTE were low and similar to placebo [83,87,91,94].

Despite the absence of a progestin, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg produced minimal stimulation of the endometrium [82,87,94]. SMART-1 and SMART-5, which evaluated endometrial hyperplasia as a primary end point, did not find an increased risk of hyperplasia with CE 0.45 mg/BZA 20 mg or CE 0.625 mg/BZA 20 mg compared with placebo (**Table 5**) [82,94]. In SMART-5, there were small but significant increases in endometrial thickness (0.17 mm with CE 0.45 mg/BZA 20 mg [$p < 0.05$] and 0.51 mm with CE 0.625 mg/BZA 20 mg [$p < 0.001$], vs 0.09 mm with placebo) but no difference between groups in proliferative endometrium [94]. No significant differences in endometrial thickness were found with CE/BZA versus placebo in SMART-1 [82].

In both SMART-1 and SMART-5 rates of vaginal bleeding among women taking either dose of CE/BZA were low (1.2 – 7.0%), similar to placebo (2.6 – 8.4%) and significantly ($p < 0.001$) less than the rate of bleeding with CE/MPA in SMART-5 (22.3%) (**Table 5**) [84,94]. Similarly, cumulative rates of amenorrhea over 13 cycles were similar to placebo and significantly ($p < 0.001$) higher than the rate in the CE/MPA arm (**Table 5**).

Across the SMART studies, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg showed no evidence of breast stimulation [86,92,94]. Mammographic breast density was not increased [86,92]. Rates of breast cancer, breast pain/tenderness and fibrocystic breast disease were no different than with placebo during the up to 2 years of follow-up [91,92,94].

**Table 5. Effect of CE/BZA on risk of endometrial outcomes and vaginal/uterine bleeding at month 12 in SMART-1 and SMART-5.**

| | SMART-1 [82,84] | | | SMART-5 [94] | | | |
|---|---|---|---|---|---|---|---|
| | CE 0.45 mg/ BZA 20 mg | CE 0.625 mg/ BZA 20 mg | PBO | CE 0.45 mg/ BZA 20 mg | CE 0.625 mg/ BZA 20 mg | PBO | CE/MPA |
| Endometrial hyperplasia, n/N (%) | 0/433 (0) | 1/414 (0.32) | 0/427 (0) | 1/335 (0.30) | 1/368 (0.27) | 1/354 (0.28) | 0/149 (0) |
| Proliferative endometrium, n/N (%) | 12/337 (3.56) | 17/314 (5.41)* | 5/317 (1.58) | 2/338 (0.59) | 1/370 (0.27) | 1/356 (0.28) | 1/153 (0.65) |
| Bleeding-related AEs, n/N (%) | 14/433 (3.2) | 5/414 (1.2) | 11/427 (2.6) | 31/445 (7.0) | 27/474 (5.7) | 40/474 (8.4) | 49/220 (22.3) |
| Cumulative amenorrhea rate in cycles 1 – 13, n/N (%) | 357/429 (83.2) | 358/410 (87.3) | 359/421 (85.3) | 312/355 (87.9)‡ | 331/390 (84.9)‡ | 318/379 (83.9) | 86/158 (54.4)§ |

*p = 0.009 vs placebo.

‡p < 0.001 vs CE/MPA.

§p < 0.001 vs PBO.

AEs: Adverse events; BZA: Bazedoxifene; CE: Conjugated estrogens; CE/MPA: Conjugated estrogens/medroxyprogesterone acetate; PBO: Placebo; SMART: Selective estrogens, Menopause, and Response to Therapy.

Furthermore, rates of breast tenderness were significantly ($p < 0.01$) lower than with CE/MPA in SMART-5 [94].

Thus, CE/BZA has shown an excellent endometrial and breast safety profile; however, it should be noted that SMART trial participants were followed for no longer than 2 years. Its safety profile over longer durations of use and follow-up requires further evaluation. Breast safety in the subpopulation of women with breast cancer risk factors also has not been evaluated.

## 8. Potential development issues

Endometrial and breast safety are key development hurdles for any new menopausal therapies. With traditional HT, estrogen(s) cannot be given without a progestin to nonhysterectomized women because unopposed systemic estrogens increase the risk of endometrial cancer [11]; however, combined estrogen-progestin therapy has been associated with an increased risk of breast cancer and related mortality in women with a uterus [15,16]. Furthermore, whereas SERMs as a class consistently have shown neutral or protective antiestrogenic activity in the breast [25,26,95], some (especially tamoxifen and lasofoxifene) exhibit adverse estrogenic stimulation of the endometrium [23,26,96]. In contrast to CE/BZA, TSEC combinations that have incorporated raloxifene, which is thought to have a neutral effect on the endometrium when given as monotherapy [25], have failed to progress through clinical development due to unacceptable endometrial safety profiles [97,98]. Vaginal estrogens are generally thought to be safe to use without a progestin in women with a uterus, although the NAMS guideline on VVA notes that 'long-term data are limited' [53]. Furthermore, vaginal estrogens are beneficial for VVA but do not address other common menopausal symptoms.

## 9. Conclusion

New and emerging menopausal therapies have the potential to fill an unmet need in the post-WHI era for effective relief of menopausal symptoms with improved safety profiles. Based on the WHI, the greatest risk appears to be associated with combined estrogen-progestin therapy; therefore, recent strategies have focused on eliminating the need for progestins either through use of topical estrogens without a progestin for VVA or by combining estrogen(s) or DHEA with potentially safer options (e.g., micronized progesterone, SERMs) to reduce endometrial stimulation.

## 10. Expert opinion

Health authorities, physicians, medical caregivers and women themselves should refocus their attention on the need for better treatment of symptoms and prevention of diseases linked to the early loss of sex steroids. Improved methods of prevention ultimately could lead to reduced disability for women in the latest stage of their lives.

The combination of an SERM with estrogens (CE/BZA) represents a new and interesting approach that obviates the need for a progestin. Based on the successful development of this combination, others are likely to follow. Preclinical and clinical data to date have found unfavorable endometrial safety profiles with other TSEC combinations that have incorporated SERMs with either CE or estradiol [97-99]. However, combinations of SERMS with other hormonal agents may

be feasible. As noted previously, DHEA/acolbifene is one such combination in development. Unlike estrogen-progestin therapies, DHEA increases androgen levels (e.g., testosterone, delta4-androstenedione), while still significantly increasing estrogens, progesterone, β-endorphin, sex-hormone binding globulin and allopregnanolone levels and decreasing cortisol levels [100,101]. As previously reviewed by one of the authors (Dr Genazzani), DHEA is a neurosteroid found at increased concentrations in the brain (relative to plasma), where it modulates release of a variety of neurotransmitters and is believed to play a role in female sexual desire, cognitive function and mood [100]. Use of DHEA to treat sexual function in postmenopausal women remains controversial due to conflicting results from randomized trials, many of which were small or had other methodologic limitations [100]. However, in a study of healthy postmenopausal women treated with oral DHEA alone, improvements in menopausal symptoms and in the frequency and enjoyment of sex were comparable to those of estradiol/dihydrogesterone over 1 year of use [101]. Whether or not DHEA has benefits over CE or estradiol when combined with SERMs as part of a TSEC requires further investigation. Data from initial studies of acolbifene/DHEA are still awaited.

Development of SERMs and TSECs – which act as estrogen agonists in some tissues and antagonists in others – has contributed greatly to our overall understanding of ER activity. Estrogens, antiestrogens and SERMs are all ER ligands, and each results in a unique estrogen-receptor conformation and gene expression profile [10,41,102,103]. For SERMs, by definition, agonist/antagonist activity is tissue selective [102]. With TSECs, combined binding of the SERM and estrogen components to the same receptor can result in a receptor-heteroligand dimer complex and cooperative stimulation of gene expression [79]. The different estrogen-receptor conformations of agonists, partial agonists and antagonists affect recruitment of coactivators versus corepressors, respectively, from the cell environment, which contributes to the differences in their gene expression profiles [102,103]. Conversely, cell-specific distribution of ER-α/ER-β and ratios of coactivators to coregulators may influence whether a ligand has agonist versus antagonist activity in a given tissue [102]. It is also noteworthy that, unlike most other SERMs, BZA has been found to downregulate ER-α protein expression by degrading the receptor in the breast and endometrium, allowing it to serve as a pure antiestrogen in two of the tissues in which estrogenic activity is of greatest concern [42,43,80,81,104]. Lessons learned from recent investigations regarding all these mechanisms points to the potential for future development of hormonal treatments with targeted tissue-selective effects of benefit in the treatment of menopausal symptoms as well as other indications (e.g., breast cancer).

New and emerging hormonal treatments for managing menopausal symptoms are likely to improve the safety profile of traditional estrogen-progestogen therapy. The ultimate goal is to get closer to the profile of the ideal menopausal therapy – that is, to relieve bothersome menopausal symptoms and reduce the risk of osteoporosis and cardiovascular disease, without increasing the risk of endometrial or breast cancer. In coming years, as products with improved safety profiles become available, an increasing number of postmenopausal women are likely to use some form of HT, primarily the ones described in this review. Women's preferences and level of compliance with these products remain to be determined.

Long-term safety data will be needed to clarify cardiovascular and breast safety profiles of all new hormonal treatments for menopausal symptoms. The large-scale WHI trial identified a number of risks associated with use of estrogens alone that were not apparent in smaller trials or observational studies; therefore, large-scale safety studies of new estrogen-containing therapies are needed to ameliorate safety concerns. Until such data are available, a conservative approach should be used in interpreting available safety data from small trials of short duration.

## Declaration of interest

BS Komm is an employee of Pfizer. JH Pickar was formerly an employee of Wyeth Research, and has received consultant fees from Wyeth/Pfizer, Besins Healthcare, Shionogi, Inc., Metagenics, and TherapeuticsMD. Medical writing support was provided by L Cerruto at Peloton Advantage, LLC, and was funded by Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


1. Avis NE, Crawford SL, McKinlay SM. Psychosocial, behavioral, and health factors related to menopause symptomatology. Womens Health 1997;3:103-20
2. Williams RE, Kalilani L, DiBenedetti DB, et al. Frequency and severity of vasomotor symptoms among peri- and postmenopausal women in the United States. Climacteric 2008;11:32-43
3. Politi MC, Schleinitz MD, Col NF. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. J Gen Intern Med 2008;23:1507-13
4. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 2005;105:1063-73
5. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc 2010;85:87-94
6. The North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause 2010;17:25-54

• **The most current guideline from NAMS on fracture prevention, including risk factor management and pharmacologic therapies.**

7. Hemminki E, Regushevskaya E, Luoto R, Veerus P. Variability of bothersome menopausal symptoms over time–a longitudinal analysis using the Estonian postmenopausal hormone therapy trial (EPHT). BMC Womens Health 2012;12:44
8. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Health Qual Life Outcomes 2005;3:47

• **Review of the considerable effects of vasomotor symptoms of menopause on quality of life, sleep, mood, memory and healthcare costs.**

9. Simon JA, Nappi RE, Kingsberg SA, et al. Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey: emotional and physical impact of vaginal discomfort on North American postmenopausal women and their partners. Menopause 2014;21:137-42

• **Recent survey of North American postmenopausal women showing that vaginal symptoms have considerable impact on sexual functioning and intimate relationships.**

10. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators – mechanisms of action and application to clinical practice. N Engl J Med 2003;348:618-29
11. The North American Menopause Society. The 2012 hormone therapy position statement of: the North American Menopause Society. Menopause 2012;19:257-71

• **The most current guideline from NAMS on the benefits and risks of hormone therapy in menopausal women.**

12. Ameye L, Antoine C, Paesmans M, et al. Menopausal hormone therapy use in 17 European countries during the last decade. Maturitas 2014. [Epub ahead of print]
13. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999-2010. Obstet Gynecol 2012;120:595-603
14. Komm BS. A new approach to menopausal therapy: the tissue selective estrogen complex. Reprod Sci 2008;15:984-92

• **Review explaining the rationale for combining estrogens with a SERM in the development of tissue selective estrogen complex therapies for menopause.**

15. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289:3243-53
16. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2010;304:1684-92
17. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol 2012;13:476-86
18. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. JAMA 2013;310:1353-68

•• **Comprehensive summary of on-therapy and postintervention effects of hormone therapy (HT) in the randomized Women's Health Initiative (WHI) trials.**

19. Food and Drug Administration. Guidance for Industry Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommended Prescribing Information for Health Care Providers and Patients Labeling. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM135336.pdf [Last accessed 13 October 2014]
20. Food and Drug Administration. Estrogen and estrogen with progestin therapies for postmenopausal women. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135318.htm [Last accessed 13 October 2014]
21. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-77

•• **Reanalysis of the WHI studies by age and years since menopause suggesting better safety profile in younger women using HT soon after menopause.**

22. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992;326:852-6
23. Jordan VC, Morrow M. Tamoxifen, raloxifene, and the prevention of breast cancer. Endocr Rev 1999;20:253-78
24. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women

treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. Breast Cancer Res Treat 2001;65:125-34

25. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355:125-37

26. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371-88

27. Christiansen C, Chesnut CH III, Adachi JD, et al. Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled Phase 3 study of postmenopausal women with osteoporosis. BMC Musculoskelet Disord 2010;11:130

- **Bazedoxifene exhibited a favorable breast and endometrial safety profile and good overall tolerability during 3 years of use in this Phase III trial.**

28. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 2008;23:1923-34

- **Bazedoxifene reduced vertebral fractures, and (in women at higher risk) nonvertebral fractures after 3 years of use in this Phase III trial.**

29. Ronkin S, Northington R, Baracat E, et al. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. Obstet Gynecol 2005;105:1397-404

30. Miller PD, Chines AA, Christiansen C, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 2008;23:525-35

31. Brisdelle [package insert]. Noven Therapeutics, LLC; Miami, FL: 2013

32. Simon JA, Portman DJ, Kaunitz AM, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause 2013;20:1027-35

- **A pair of Phase III trials in which paroxetine produced a modest but significant reduction in VMS frequency/severity through 2 years of treatment.**

33. Portman DJ, Kaunitz AM, Kazempour K, et al. Effects of low-dose paroxetine 7.5 mg on weight and sexual function during treatment of vasomotor symptoms associated with menopause. Menopause 2014;21:1082-90

34. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-12

35. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33

36. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-27

37. North American Menopause Society. HT prescriptions: a continued slow decline in 2010 (except for vaginal estrogens). Available from: http://www.menopause.org/publications/clinical-practice-materials/Htstatistics [Last accessed 9 May 2014]

38. Power ML, Anderson BL, Schulkin J. Attitudes of obstetrician-gynecologists toward the evidence from the Women's Health Initiative hormone therapy trials remain generally skeptical. Menopause 2009;16:500-8

39. American College of Obstetricians and Gynecologists. Committee opinion no. 532: compounded bioidentical menopausal hormone therapy. Available from: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Compounded-Bioidentical-Menopausal-Hormone-Therapy [Last accessed 21 August 2014]

- **A practice bulletin from ACOG noting the lack of evidence of superiority for compounded bioidentical hormones versus conventional HT.**

40. Pickar JH, MacNeil T, Ohleth K. SERMs: progress and future perspectives. Maturitas 2010;67:129-38

41. Chang KC, Wang Y, Bodine PV, et al. Gene expression profiling studies of three SERMs and their conjugated estrogen combinations in human breast cancer cells: insights into the unique antagonistic effects of bazedoxifene on conjugated estrogens. J Steroid Biochem Mol Biol 2010;118:117-24

42. Ethun KF, Wood CE, Register TC, et al. Effects of bazedoxifene acetate with and without conjugated equine estrogens on the breast of postmenopausal monkeys. Menopause 2012;19:1242-52

43. Ethun KF, Wood CE, Cline JM, et al. Endometrial profile of bazedoxifene acetate alone and in combination with conjugated equine estrogens in a primate model. Menopause 2013;20:777-84

44. Axlund SD, Sartorius CA. Progesterone regulation of stem and progenitor cells in normal and malignant breast. Mol Cell Endocrinol 2012;357:71-9

45. Liang Y, Benakanakere I, Besch-Williford C, et al. Synthetic progestins induce growth and metastasis of BT-474 human breast cancer xenografts in nude mice. Menopause 2010;17:1040-7

46. Brisken C. Progesterone signalling in breast cancer: a neglected hormone coming into the limelight. Nat Rev Cancer 2013;13:385-96

47. Rivas MA, Venturutti L, Huang YW, et al. Downregulation of the tumor-suppressor miR-16 via progestin-mediated oncogenic signaling contributes to breast cancer development. Breast Cancer Res 2012;14:R77

48. Tkach M, Rosemblit C, Rivas MA, et al. p42/p44 MAPK-mediated Stat3Ser727 phosphorylation is required for progestin-induced full activation of Stat3 and breast cancer growth. Endocr Relat Cancer 2013;20:197-212

49. Osphena [package insert]. Shionogi, Inc; Florham Park, NJ: 2013

50. European Medicines Agency. Applications for new human medicines under evaluation by the committee for medicinal products for human use. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/07/WC500169655.pdf [Last accessed 10 July 2014]

51. Duavee [package insert]. Wyeth Pharmaceuticals, Inc., A subsidiary of Pfizer, Inc; Philadelphia, PA: 2013

52. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2006(4):CD001500

- **Cochrane meta-analysis concluding that all delivery methods for vaginal estrogens help relieve symptoms of VVA.**

53. The North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause 2013;20:888-902

- **Current position statement from NAMS regarding individualized treatment of VVA with hormonal and nonhormonal strategies based on symptom severity, treatment effectiveness/safety and patient preference.**

54. TherapeuticsMD. NYSE MKT: TXMD Corporate Overview. Available from: http://www.therapeuticsmd.com/presentations.aspx [Last accessed 13 May 2014]

55. ClinicalTrials.gov. Safety & efficacy WC3011 in the treatment of vulvovaginal atrophy in postmenopausal women (VENUS) NCT01400776. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01400776?term=vulvovaginal+atrophy&rank=1 [Last accessed 9 May 2014]

56. ClinicalTrials.gov. Evaluate long-term safety and efficacy WC3011 NCT01455597. Available from: http://www.clinicaltrials.gov/ct2/show/study/NCT01455597?term=vulvovaginal+atrophy&rank=2 [Last accessed 9 May 2014]

57. ClinicalTrials.gov. Study to evaluate safety & efficacy of WC3011 in postmenopausal women with dyspareunia. NCT01845649. Available from: http://www.clinicaltrials.gov/ct2/show/study/NCT01845649?term=vulvovaginal+atrophy&rank=8 [Last accessed 9 May 2014]

58. ClinicalTrials.globe24g.com. Evaluate long-term safety and efficacy WC3011. NCT01455597 Available from: http://clinicaltrials.globe24h.com/0/0/symptoms-and-general-pathology/a/atrophy/2011/10/17/nct01455597-evaluate-long-term-safety-and-efficacy-wc3011-warner-chilcott.shtml [Last accessed 9 May 2014]

59. ClinicalTrials.gov. Multicenter study to evaluate safety and efficacy of WC3011 in postmenopausal women. NCT01816139 Available from: http://clinicaltrials.gov/ct2/show/NCT01816139 [Last accessed 9 May 2014]

60. Business Wire. TherapeuticsMD reports positive results of rabbit irritation study for its estradiol vaginal capsule VagiCap™ (TX 004-HR) for treatment of vulvar vaginal atrophy (VVA) [press release]. Available from: http://www.businesswire.com/news/home/20140407005470/en/TherapeuticsMD-Reports-Positive-Results-Rabbit-Irritation-Study#.U3OtSPldX9Z [Last accessed 13 May 2014]

61. TherapeuticsMD. TherapeuticsMD reports positive PK study results for its estradiol vaginal capsule VagiCap™ (TX 12-004-HR) for treatment of vulvar vaginal atrophy (VVA) [press release]. Available from: http://www.therapeuticsmd.com/pressreleases.aspx [Last accessed 13 May 2014]

62. PBR Contract Research & Services Clinical Trial. TherapeuticsMD reports positive PK study results for vulvar vaginal atrophy drug [press release]. Available from: http://clinicaltrials.pharmaceutical-business-review.com/news/therapeuticsmd-reports-positive-pk-study-results-for-vulvar-vaginal-atrophy-drug-290114-4167592 [Last accessed 9 May 2014]

63. Food and Drug Administration. Compounded menopausal hormone therapy questions and answers. Available from: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm183088.htm [Last accessed 14 May 2014]

64. American College of Obstetricians and Gynecologists. Practice bulletin no. 141: management of menopausal symptoms. Obstet Gynecol 2014;123:202-16

- **A 2014 practice bulletin from ACOG regarding various therapies for managing vasomotor and vaginal symptoms of menopause.**

65. Business Wire. TherapeuticsMD to present the design of its REPLENISH trial at the International Menopause Society's 14th World Congress [press release]. Available from: http://www.businesswire.com/news/home/20140501006446/en/TherapeuticsMD-Present-Design-REPLENISH-Trial-International-Menopause#.U3OxOPldX9Z [Last accessed 12 May 2014]

66. Pickar JH, Bon C, Amadio JM, Bernick B. Pharmacokinetics of the first combination 15ß-estradiol/progesterone capsule in clinical development for hormone therapy [abstract P-81]. Presented at: annual Meeting of the North American Menopause Society; 9 – 12 October 2013; Grapevine, TX

67. ClinicalTrials.gov. A safety and efficacy study of the combination estradiol and progesterone to treat vasomotor symptoms (REPLENISH) NCT01942668. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01942668?term=REPLENISH&rank=1 [Last accessed 21 April 2014]

68. ClinicalTrials.gov. Dehydroepiandrosterone (DHEA) + acolbifene against vasomotor symptoms (hot flushes) in postmenopausal women. NCT01452373. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01452373?term=acolbifene&rank=1 [Last accessed 9 May 2014]

69. Femivia™. Endoceutics. Available from: http://www.endoceutics.com/our-products/femivia8482/?no_cache=1&sword_list[0]=femivia [Last accessed 12 May 2014]

70. Labrie F. DHEA, important source of sex steroids in men and even more in women. Prog Brain Res 2010;182:97-148

71. Goss PE, Qi S, Cheung AM, et al. The selective estrogen receptor modulator SCH 57068 prevents bone loss, reduces serum cholesterol and blocks estrogen-induced uterine hypertrophy in ovariectomized rats. J Steroid Biochem Mol Biol 2004;92:79-87

72. Berger L, El-Alfy M, Martel C, Labrie F. Effects of dehydroepiandrosterone, Premarin and Acolbifene on histomorphology and sex steroid receptors in the rat vagina. J Steroid Biochem Mol Biol 2005;96:201-15

73. Pelletier G, Ouellet J, Martel C, Labrie F. Androgenic action of dehydroepiandrosterone (DHEA) on

nerve density in the ovariectomized rat vagina. J Sex Med 2013;10:1908-14

74. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 2010;17:480-6

•• **Phase III study showing ospemifene reduced vaginal dryness and dysparneunia in postmenopausal women.**

75. Portman DJ, Bachmann GA, Simon JA. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause 2013;20:623-30

•• **Phase III study showing ospemifene's effects on percentages of parabasal and superficial cells, vaginal pH and severity of dyspareunia.**

76. Goldstein SR, Bachmann GA, Koninckx PR, et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric 2014;17:173-82

• **Contains safety results, including endometrial safety, for ospemifene through 1 year of use.**

77. Simon JA, Lin VH, Radovich C, Bachmann GA. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013;20:418-27

• **Contains safety results, including endometrial safety, for ospemifene through 1 year of use.**

78. Kharode Y, Bodine PV, Miller CP, et al. The pairing of a selective estrogen receptor modulator, bazedoxifene, with conjugated estrogens as a new paradigm for the treatment of menopausal symptoms and osteoporosis prevention. Endocrinology 2008;149:6084-91

79. Liu S, Han SJ, Smith CL. Cooperative activation of gene expression by agonists and antagonists mediated by estrogen receptor heteroligand dimer complexes. Mol Pharmacol 2013;83:1066-77

• **Introduces the concept of estrogen receptor (ER) agonists and antagonists forming heteroligand dimer complexes that provide cooperative gene activation, with implications for CE/BZA mechanism of action.**

80. Lewis-Wambi JS, Kim H, Curpan R, et al. The selective estrogen receptor modulator bazedoxifene inhibits hormone-independent breast cancer cell growth and down-regulates estrogen receptor alpha and cyclin D1. Mol Pharmacol 2011;80:610-20

• **Preclinical study most noteworthy for demonstration of ER degradation in the breast by bazedoxifene.**

81. Wardell SE, Nelson ER, Chao CA, McDonnell DP. Bazedoxifene exhibits antiestrogenic activity in animal models of tamoxifen-resistant breast cancer: implications for treatment of advanced disease. Clin Cancer Res 2013;19:2420-31

82. Pickar JH, Yeh IT, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril 2009;92:1018-24

•• **Phase III data on endometrial safety of CE/BZA (SMART-1 trial).**

83. Lobo RA, Pinkerton JV, Gass ML, 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;92:1025-38

84. Archer DF, Lewis V, Carr BR, et al. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. Fertil Steril 2009;92:1039-44

85. Lindsay R, Gallagher JC, Kagan R, et al. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 2009;92:1045-52

•• **Phase III study supporting CE/BZA's beneficial effects on bone (SMART-1).**

86. Harvey JA, Pinkerton JV, Baracat EC, et al. Breast density changes in a randomized controlled trial evaluating bazedoxifene/conjugated estrogens. Menopause 2013;20:138-45

• **Ancillary study showing no increase in breast density with CE/BZA (SMART-1).**

87. Pinkerton JV, Utian WH, Constantine GD, et al. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. Menopause 2009;16:1116-24

•• **Phase III study showing CE/BZA reduced frequency and severity of hot flushes in women with vasomotor symptoms (SMART-2).**

88. Utian W, Yu H, Bobula J, et al. Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. Maturitas 2009;63:329-35

89. Kagan R, Williams RS, Pan K, et al. 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;17:281-9

• **Phase III study describing effects of CE/BZA on vulvar-vaginal atrophy (SMART-3).**

90. Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. Climacteric 2010;13:132-40

91. Mirkin S, Komm BS, Pan K, Chines AA. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. Climacteric 2013;16:338-46

92. Pinkerton JV, Harvey JA, Pan K, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstet Gynecol 2013;121:959-68

93. Pinkerton JV, Pan K, Abraham L, et al. Sleep parameters and health-related quality of life with bazedoxifene/conjugated estrogens: a randomized trial. Menopause 2014;21:252-9

• **Substudy of a Phase III trial showing that CE/BZA improves sleep and menopause-specific health-related quality of life.**

94. Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab 2014;99:E189-98

•• **Phase III trial supporting CE/BZA's endometrial safety and beneficial effects on BMD (SMART-5).**

95. LaCroix AZ, Powles T, Osborne CK, et al. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. J Natl Cancer Inst 2010;102:1706-15

96. McClung MR, Siris E, Cummings S, et al. Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. Menopause 2006;13:377-86

97. Stovall DW, Utian WH, Gass ML, et al. The effects of combined raloxifene and oral estrogen on vasomotor symptoms and endometrial safety. Menopause 2007;14:510-17

98. Carranza-Lira S, Gooch AL, Saldivar N, Osterwalder MS. Climacteric symptom control after the addition of low-dose esterified conjugated estrogens to raloxifene standard doses. Int J Fertil Womens Med 2007;52:93-6

99. Peano BJ, Crabtree JS, Komm BS, et al. Effects of various selective estrogen receptor modulators with or without conjugated estrogens on mouse mammary gland. Endocrinology 2009;150:1897-903

100. Pluchino N, Drakopoulos P, Bianchi-Demicheli F, et al. Neurobiology of DHEA and effects on sexuality, mood and cognition. J Steroid Biochem Mol Biol 2014. [Epub ahead of print]

101. Genazzani AR, Stomati M, Valentino V, et al. Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality. Climacteric 2011;14:661-8

102. Huang P, Chandra V, Rastinejad F. Structural overview of the nuclear receptor superfamily: insights into physiology and therapeutics. Annu Rev Physiol 2010;72:247-72

103. Berrodin TJ, Chang KC, Komm BS, et al. Differential biochemical and cellular actions of Premarin estrogens: distinct pharmacology of bazedoxifene-conjugated estrogens combination. Mol Endocrinol 2009;23:74-85

104. Kulak J Jr, Fischer C, Komm B, Taylor HS. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology 2011;152:3226-32

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