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APPLICATION NUMBER:

022247Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22247
Priority or Standard	Standard
Submit Date(s)	September 26, 2012
Received Date(s)	October 3, 2012
PDUFA Goal Date	October 3, 2013
Division / Office	DBRUP/ODE III/OND/CDER
Reviewer Name(s)	Marcea Whitaker, M.D. Stephen Bienz, M.D. Gerald Willett, M.D. Stephen Voss, M.D. Theresa Kehoe, M.D.
Review Completion Date	June 5, 2013
Established Name	Conjugated estrogens/ bazedoxifene
(Proposed) Trade Name	Duavee
Therapeutic Class	Estrogen/SERM combination
Applicant	Wyeth
Formulation(s)	Coated Tablets
Dosing Regimen	One tablet daily (0.625/20mg, 0.45/20mg)
Indication(s)	1) Treatment mod to severe vasomotor symptoms associated with menopause 2) Treatment mod to severe vulvar and vaginal atrophy associated with menopause 3) Prevention of postmenopausal osteoporosis
Intended Population(s)	Postmenopausal women with intact uterus

Template Version: March 6, 2009

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(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Treatment of Vasomotor Symptoms:
From the clinical perspective, the once daily bazedoxifene/conjugated estrogens combination BZA 20/CE 0.45 for the treatment of moderate and severe vasomotor symptoms in women with a uterus should be approved. This recommendation is based on an acceptable decrease in the number and severity of hot flushes at Week 4 and Week 12. The BZA 20/CE 0.625 dose is not supported (b) (4)

Prevention of Postmenopausal Osteoporosis:
From the clinical perspective, once daily BZA 20/CE 0.45 for the prevention of osteoporosis in women with a uterus should be approved. This recommendation is based on demonstration of an acceptable increase in bone mineral density at 24 months. A limitation of use should be included to acknowledge the lack of fracture efficacy (b) (4)
The BZA 20/CE 0.625 dose is not supported (b) (4)

Treatment of Vulvar and Vaginal Atrophy:
From the clinical perspective, the treatment of moderate and severe vulvar and vaginal atrophy should receive a complete response. (b) (4)

Deficiencies include:
(b) (4)

Items needed to address the deficiencies:
(b) (4)

(b) (4)

1.2 Risk Benefit Assessment

This BZA/CE combination is being developed to treat symptoms associated with menopause. The estrogen component of the product provides the symptom relief and bone density increases supporting efficacy. The bazedoxifene component of the product provides endometrial protection against estrogen effects on the uterus. In this regard, bazedoxifene exhibits a narrow therapeutic window. Efficacy data for all indications show an attenuation of effect as the dose of BZA increases in the BZA/CE product. In the 2-year study (303), BZA 10 mg/CE showed greater efficacy compared to BZA 20/CE or BZA 40/CE in a dose-dependent manner, however, the BZA 20 mg dose was the lowest effective dose needed for endometrial protection. This narrow therapeutic window contributes substantially to the risk benefit assessment.

Retention of source documentation was a major review issue. Due to natural disaster, clerical errors, or unknown random-appearing events, source documentation was partially or completely missing in 8.1% of subjects in Study 303, 1.5% of subjects in Study 305, 8% of subjects in Study 306, and 0.7% of subjects in Study 304. In the two Brazilian sites (sites 447 and 450 of Study 303), the missing data rate was as high as 10.3%. These rates of missing source documentation far exceed rates generally seen by the Agency. Prior to NDA submission, the Agency attempted to define the magnitude and determine the specific documents that were missing or destroyed. These data were submitted 4 months after NDA submission (February 19, 2013). (b) (4) Removal of subjects with missing source documentation did not adversely affect the PMO or VMS indications.

Study conduct issues including good clinical procedures and adverse event reporting were noted during the clinical program and affected mainly Study 303 and the PMO indication. Monitoring of the Brazilian sites (447 and 450 of study 303) and subsequent 3rd party audits uncovered subjects with missing source documentation at various sites as discussed. In addition, some endometrial biopsy data were not in the clinical database. For some patients, slides and blocks from unscheduled were identified for which there were no data in the database. The study database had to be reopened in order to add these data from the pathology worksheets. Slides with no available worksheets were read by independent pathologists long after the study closed. Mammograms for site 447 (76 subjects) and 450 (35 subjects) were lost in transit due to customs detainment. On May 23 and 29, 2013, the sponsor further submitted changes to the clinical study reports for studies 303, 304, 305, 306, 3307, and 4000. Substantial review of these study reports and their potential impact on approvability was not possible prior to finalization of this review.

The quality of adverse event reporting and other safety information was poor (b) (4) Several internal and external audits were performed which uncovered un-coded and unreported adverse events. Additional adverse events were recently reported at site 447 (May 23, 2013), one of which may represent an additional event of stroke. Of note, sites 447 and 450 enrolled one-third of the total population for Study 303. If significant issues are found during the ongoing inspection of site 447, the validity of data from the Brazilian sites may be compromised and data from these sites may not be allowed. A preliminary analysis of BMD data excluding sites 447 and 450 (although not excluding all subjects with missing data across all sites) show similar results and exclusion of these sites will likely not effect PMO indication. The VMS indication does not rely on Study 303 and will not be affected.

Vulvar Vaginal Atrophy:

(b) (4) As a result, the indication for treatment of moderate to severe vulvar and vaginal atrophy is not supported and should not be approved.

Vasomotor Symptoms:

The indication for the treatment of moderate to severe vasomotor symptoms was based on pivotal trial 305. Significant decreases in the mean number and severity of moderate and severe hot flushes at Weeks 4 and 12 (co-primary endpoints) were seen in both BZA/CE groups ($p<0.001$). BZA 20/CE 0.45 and BZA 20/CE 0.625 doses led to a mean reduction in hot flushes of -7.6 and (b) (4) per day, respectively at Week 12, with placebo-subtracted changes of -2.7 and (b) (4), respectively, which exceed the > 2 hot flush/day criterion referenced in the 2003 Guidance. (b) (4) Study 303 showed numerical decreases in number and severity of hot flushes in both dose groups but due to the step-down procedure used, this study can only provide support for the VMS indication. In the reviewer's opinion, the magnitude of effect in reduction in hot flushes with BZA/CE is numerically lower than other approved conjugated estrogen/progestin preparations (e.g. Prempro with mean decreases of -10.8 hot flushes/day and placebo-subtracted decreases of -4.8) but the effect is still clinically significant.

Prevention of PMO:

The mean increase in BMD at Month 24 (key secondary endpoint) following BZA 20/CE 0.45 ranged between 1.64 and 1.72% (placebo-subtracted difference of 3.62% and

3.71%) for subgroup I (those < 5 years postmenopausal) and subgroup II (those > 5 years postmenopausal) respectively, and following BZA 20/CE 0.625 mean differences ranged between (b) (4) (placebo-subtracted difference of (b) (4) for subgroup I and II, respectively, When BZA 20/CE 0.45 and BZA 20/CE 0.625 doses are compared at Month 24 (Study 303), no dose relationship at the lumbar spine was seen for the subgroup of patients less than 5 years menopausal (Subgroup II). Twelve month data from the supportive study (Study 3307) did show a small dose effect in this same population. Similarly, for the subgroup who were menopausal for at least 5 years (Subgroup I), despite a slightly greater numerical BMD difference with the higher dose (+0.50%), there was considerable overlap in the confidence intervals suggesting no real difference between the doses. Dose selection should favor the lowest effective dose and should be balanced with the safety profile.

Numerically greater increases in lumbar spine BMD were noted in the CE/MPA group at 12 months in Study 3307 but all groups (CE/MPA, BZA 20/CE 0.625 and BZA 20/CE 0.45) showed statistical significance over placebo (p< 0.001). In the opinion of the reviewer other approved products provide context to the modest maximal lumbar spine changes of (b) (4) (placebo-subtracted, (b) (4) seen following administration of BZA 20/CE 0.625 at 24 months. The study populations differed in mean age and entry criteria (T-score, years since menopause) but were generally healthy postmenopausal women and mnay had at least 1 risk factor for osteoporosis. The HOPE trial (conjugated estrogen 0.625 and MPA 2.5 mg) showed greater mean changes in lumbar spine BMD of 3.28% (placebo-subtracted, 5.73%) at 2 years. Two-year data using BZA 20 monotherapy (Study 300) led to mean lumbar spine changes of only 1.41% (b) (4) While the interaction between BZA and CE is not clear, it is evident that the combination of BZA and conjugated estrogen does not exert an additive or synergistic effect on bone. In fact, the majority of the BMD effect can be attributed to conjugated estrogen and bazedoxifene actually takes away from its effect. BZA/CE provides similar lumbar spine BMD changes as raloxifene 60 mg. In Study 303, the raloxifene 60 mg arm showed a mean LS change of 0.75% (placebo-subtracted 2.2%) which was similar to rate reported in the EVISTA label (1.8-2.4%, placebo subtracted). It is the reviewer's opinion that the BZA/CE doses provide comparable efficacy to Evista and is a viable option for an alternative therapy in the prevention of osteoporosis from an efficacy perspective.

In addition to the effect on BMD, fracture efficacy should be considered. Other than the studies submitted to support this NDA, there are no data describing the effect of BZA plus conjugated estrogen on bone. There is sufficient epidemiologic evidence on fracture prevention with conjugated estrogen but these are limited to doses of 0.625 mg. While BZA 20 mg monotherapy (b) (4) showed modest lumbar BMD changes (mean change +1.41%) and a 40% decrease in vertebral fractures, (b) (4) the effect of the combination product, BZA/CE, on fracture reduction is unknown. Due to the decrease in BMD seen when both products are

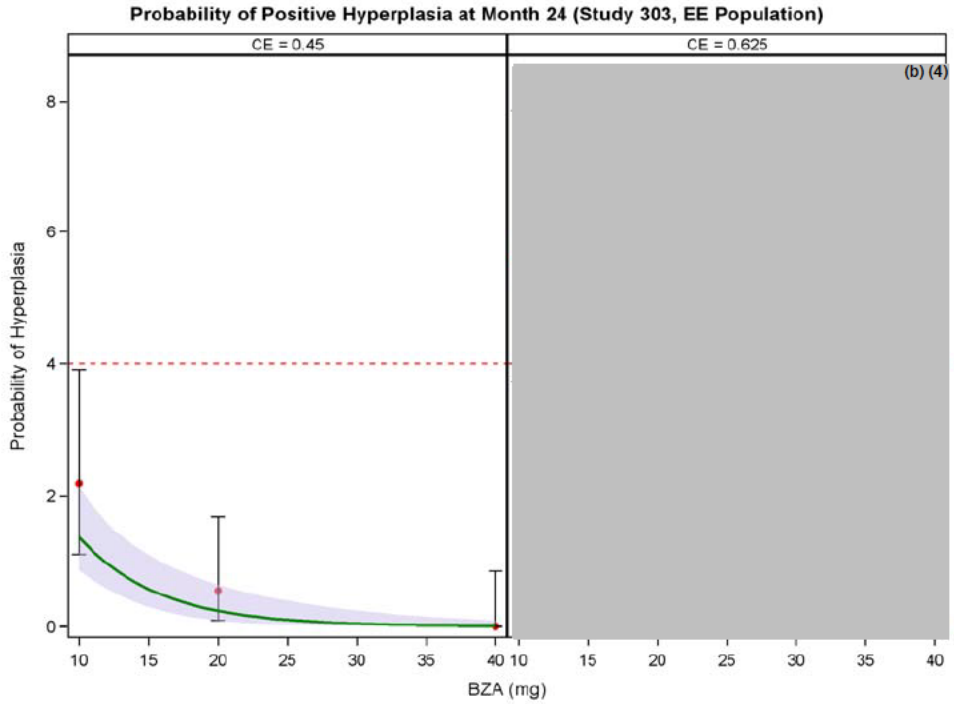
combined, the bridge between BMD change and fracture efficacy for both proposed doses becomes compromised. In fact, BZA may take away enough of conjugated estrogen's effect to change the overall efficacy profile. This becomes a greater issue if BZA 20/CE 0.45 is the only approved dose. (b) (4) (b) (4) While a fracture study is not required or recommended at this time, one may be useful in addressing this outstanding question.

Safety:
The safety profile of conjugated estrogens and estrogen agonist/antagonists are well documented. The clinical trials supporting this NDA did not reveal new safety concerns.

Endometrial safety: The role of bazedoxifene in this combination product is to provide endometrial protection. Therefore, all indications for BZA/CE hinge on an acceptable degree of endometrial protection (1%, with one-sided 95% CI of 4%). Phase 2 dose-finding comparing BZA 5, 10, and 20 mg, in combination with conjugated estrogen 0.625 or 0.3 mg, proved that BZA 20 mg was the lowest dose that provided sufficient endometrial protection. Study 304, which used Formulation C and had decreased BZA bioavailability, highlights the safety risk of having too little BZA exposure. Formulation C had lower bioavailability following single dosing (18-25%) and multiple dosing (up to 36%). (b) (4) As a result, subjects with significantly higher clearance to BZA due to intrinsic or extrinsic factors may be at risk of underexposure and more likely to develop hyperplasia. (b) (4) .

Figure 1 shows the probability of hyperplasia at Month 24 from Study 303. (b) (4) If BZA exposure were decreased for any reason (formulation issues, inconsistent manufacturing, food effects, drug-drug interactions, etc.) or any combination of reasons, the risk of hyperplasia could be sufficiently higher and exceed acceptable rates. Figure 1 does not represent the worst case scenario of combining Month 24 data from both Study 303 and 304. No hyperplasia concerns were noted with the BZA/CE 0.45 dose.

Figure 1: Probability of Positive Hyperplasia at Month 24 (Study 303, EE Population)



Source: Clinical Pharmacology Reviewer

(b) (4)

CV/VTE risk: Estrogen products and estrogen agonist/antagonist products are associated with an increased risk of thrombotic events. In the Women's Health Initiative study, the risk of VTE in the WHI estrogen alone substudy was 28 per 10,000 women-years for CE 0.625 mg compared to 21 per 10,000 women-years for placebo. In the (b) (4) the rate of VTE, defined as DVT, PE, and retinal vein thrombosis, in the three year fracture Trial 301 was 35 per 10,000 woman-years for BZA 20 mg daily compared to 22 per 10,000 woman years for raloxifene and 17 per 10,000 woman years for placebo. The rate of stroke in Study 301 was 37 per 10,000 woman-years for BZA 20 mg daily compared to 30 per 10,000 woman years for placebo.

In this NDA, VTE rates in Trial 303 were 7 per 10,000 woman years in all CE/BZA treatment groups combined. Stroke rates in Trial 303 were 7 per 10,000 woman years in all CE/BZA treatment groups combined. Other trials in the CE/BZA development program generally show similar results. In addition, low VTE rates are reported for CE/MPA, bazedoxifene monotherapy, raloxifene, and placebo treatment groups in CE/BZA trials supporting this NDA.

The decreased rates of VTE and stroke seen in the CE/BZA program cannot be explained and the interaction between BZA and CE is unknown. Based on what is known, these results/findings do not negate the risk of VTE/CVA following the administration of BZA/CE and warnings for similar products should be applied in labeling.

Formulation Issues:
The sponsor also has not adequately demonstrated bridging amongst the formulations used in the clinical program to the final to-be-marketed formulation and the manufacturing of the to-be-marketed product has been inconsistent. Ongoing review of the manufacturing process (b) (4) of the tablet and the current recommendation from the Office of Compliance district office is to issue a withhold. A final determination has not been made. (b) (4)

Special Populations:
BZA/CE was only studied in subjects less than age 75 and no restrictions in labeling have been proposed by the sponsor. Based on studies conducted for the bazedoxifene monotherapy (b) (4) (b) (4) Study 121-US), age did have an effect on the pharmacokinetics of BZA. Compared to the age 51-64 years group, BZA AUC increased from 54% in the 65-74 years group and 158% in those >75 years. While subjects over 75 years may not be a population to use BZA/CE for the VMS indication, patients treated for the prevention of osteoporosis may exceed age 75. Since no data exist for BZA/CE in patients over 75, this reviewer recommends limiting the PMO indication to those < 75 years of age. There are no data to warrant a contraindication.

The effect of BZA/CE on renal function was not evaluated. Data from (b) (4) Study 121-US evaluated renal impairment following BZA monotherapy in the 35-75 year age group. Given the mechanism of metabolism and excretion for bazedoxifene, renal impairment is not expected to affect pharmacokinetics. However, data from severe renally impaired postmenopausal patients (n=2) showed a 69% increase in BZA AUC following BZA 20 mg. Due to the low number of subjects, it is not possible to conclude that renal impairment affects BZA exposure. There is a theoretical risk that renal impairment would decrease renal clearance of BZA/CE and increase the VTE risk. The sponsor has proposed not to recommend use in patients with renal impairment. The available data do not support a contraindication in this population.

In patients with hepatic impairment, the AUC increased by 143%, 109%, and 268% in mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Class) compared to healthy subjects. Use is not recommended in patients with hepatic impairment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies (REMS) are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No clinical postmarketing requirements and commitments are recommended. However, clinical would support a postmarketing requirement for renal impairment if deemed appropriate by the clinical pharmacology team.

2 Introduction and Regulatory Background

2.1 Product Information

Conjugated Estrogens/Bazedoxifene (BZA/CE) tablet is a fixed dose combination product. Conjugated estrogens are of equine origin and are a mixture of multiple estrogens including sodium estrone sulfate, sodium equilin sulfate, and sodium sulfate conjugates. (b) (4) BZA is a selective estrogen receptor modulator (SERM) with tissue selective estrogen receptor agonist and antagonist activity at various organs. (b) (4) he proposed to-be-marketed tablet strengths are BZA 20/CE 0.45 mg and BZA 20/CE 0.625 mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple products approved for each of the three proposed indications and include estrogen alone, and estrogen/progestin combination products in various formulations (tablets, creams, transdermal and vaginal rings). See Appendix 9.4 (Table 123, Table 124, and Table 125) for full listings. Bazedoxifene/conjugated estrogens would be the first product combining estrogen and a selective estrogen receptor modulator for any indication.

2.3 Availability of Proposed Active Ingredient in the United States

Conjugated estrogens have been marketed since 1942 within the United States for treatment of menopausal symptoms and later for the prevention of postmenopausal osteoporosis indications.

Bazedoxifene is not approved in the United States. (b) (4) BZA is approved in Europe as Conbriza (20 mg) and in other markets, including Japan, for treatment of osteoporosis.

2.4 Important Safety Issues With Consideration to Related Drugs

Estrogen and Estrogen/Progestins:

Unopposed estrogen increases the risk of endometrial cancer in a woman with a uterus. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. The BZA in this combination product is a substitute for progestin and is intended to provide endometrial protection.

On July 17, 2002, after an average follow-up of 5.2 years, the conjugated estrogens (0.625 mg Premarin®) plus medroxyprogesterone acetate (2.5 mg MPA) clinical trial of the Women's Health Initiative (WHI) study was stopped early because of an increased risk of breast cancer (hazard ratio [HR] of 1.26 with a 95% CI of 1.00-1.59), increased risk of stroke (HR of 1.41 with a 95% CI of 1.07-1.85), increased risk of coronary heart disease (HR of 1.29 with a 95% CI of 1.02-1.63), increased risk of probable dementia (HR of 2.05 with a 95% CI of 1.21-3.48), and a decreased risk of hip fracture (HR of 0.66 with a 95% CI of 0.45-0.98).

The risk and benefit information available from this WHI study (2002) prompted changes in labeling for estrogen class drug products including, but not limited to, the addition of a boxed warning to all estrogen plus progestin product labels and the expansion of the existing boxed warning in all estrogen alone product labels to include the increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis reported in the estrogen plus progestin WHI study. In addition, boxed warning information states that "---in the absence of comparable data, these risks should be assumed to be similar" for "other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestin", and that "---estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women."

On March 1, 2004, after an average follow-up of 6.8 years, the conjugated estrogens alone clinical trial of the WHI study was stopped because the use of conjugated estrogens alone (0.625 mg Premarin®) increased the risk of stroke (estimated hazard ratio [HR] of 1.39 with a 95% confidence interval [CI] for conjugated estrogens versus placebo of 1.10-1.77). Other findings in the conjugated estrogens alone clinical trial included a decreased risk of hip fracture (HR of 0.61 with a 95% CI of 0.41-0.91), no

effect on coronary heart disease (HR of 0.91 with a 95% CI of 0.75-1.12), a reduction in breast cancer (HR of 0.77 with a 95% CI of 0.59-1.01), an increased risk for probable dementia (HR of 1.49 with a 95% CI of 0.83-2.66), and no decrease in mild cognitive impairment (HR of 1.34 with a 95% CI of 0.95-1.89).

The risk and benefit information available in the estrogen alone WHI study in year 2004 prompted changes in labeling for estrogen class drug products including, but not limited to, the expansion of the boxed warning to include the reported increased risk of stroke in the estrogen alone WHI study.

Risk information available in the Women's Health Initiative Memory Study (WHIMS) in years 2003 and 2004 prompted additional changes in labeling for estrogen class drug products to include the reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older. WHIMS findings for both the estrogen alone substudy and the estrogen plus progestin substudy were added to the boxed warning, and the clinical studies, warnings, and precautions sections of estrogen class labeling.

Estrogen Agonist/Antagonists (SERMs):
Estrogen Agonist/Antagonists, including raloxifene, have shown an increased risk of venous thromboembolic events (VTEs), including DVTs, PEs and strokes. The risk appears to reflect a pro-coagulant state. As a result, these products contain black boxed warnings for the risk of VTEs, pulmonary emboli, deep vein thrombosis and death due to stroke.

(b) (4)

In the 3-year BZA monotherapy fracture study (Study 301) (b) (4) results showed a 2-fold increase in venous thromboembolic events and stroke in both the BZA 20 mg and 40 mg dose groups compared to raloxifene, despite comparable vertebral fracture efficacy. See Table 1. Superficial thrombophlebitis rates were also increased in the BZA groups. Assessments were further complicated by concomitant anti-thrombotic therapy in a large number of subjects. (b) (4)

Table 1: Safety Events of Concern – BZA Monotherapy – Study 301 (3-year fracture study)

Adverse Event	BZA 20 mg	BZA 40 mg	Raloxifene	Placebo
VTE	0.8%	0.8%	0.5%	0.4%
Stroke	0.9%	1.1%	0.5%	0.7%
Superficial thrombophlebitis	1.6%	1.9%	1.4%	1.2%
(b) (4)				

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial Pre-IND meetings for the combination product (under IND 62288 in Division of Metabolic and Endocrine Products and IND (b) (4) in Division of Bone, Reproductive and Urologic Products were held in November 2000 and predates the current version of the draft guidance *"Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms"* (dated 2003). These meetings established that two studies would be needed to demonstrate endometrial safety, and two-year BMD data would be required along with fracture data to support the prevention of PMO indication. The optimum dose would need to provide both uterine and bone protection.

An End-of-Phase 2 meeting (July 25, 2001), stressed the importance of defining the lowest effective dose to prevent endometrial hyperplasia. Communication on October 9, 2001, outlined the need for bone histomorphometry in a subset of women and recommended (b) (4) . Only the lowest effective dose for vasomotor symptoms (VMS) and VVA would be approved. Further communication on November 1, 2001, allowed for fracture data from the BZA monotherapy program to serve as supportive data provided the same doses were studied and the BMD results were consistent between studies.

There were two Special Protocol Assessments (SPAs). The first was specific to study 304 (dated January 7, 2005) and included comments for study 305 and 306. Study 304 was to be the confirmatory endometrial study. For the endometrial protection claim, the sponsor had to demonstrate an incidence rate of endometrial hyperplasia of ≤ 1% with an upper bound of the one-sided 95% confidence interval ≤ 4%. For Study 303, which was ongoing at the time the Guidance Document published, two pathologists (instead of three defined in the current guidance) would be acceptable for endometrial biopsy readings. (b) (4)

Due to formulation issues and decreased BZA bioavailability in Study 304, a second SPA specific to study 3307 was issued on October 10, 2008, which allowed Study 3307 to replace Study 304. Additional meetings were held on February 18, 2010 (CMC Pre-NDA) and September 27, 2011 (Administrative). A Type C meeting (under IND 62288) was held on September 14, 2012, to discuss the amount of missing data and incomplete retention of records with Office of Scientific Investigations (OSI). At conclusion of the meeting, there remained outstanding questions regarding which records were missing for which subjects. Additional site level data, third party audit reports and information on monitoring and oversight were requested.

2.6 Other Relevant Background Information

2.6.1 Formulation/Bioavailability Issue

Over the 10-year period of drug development, several formulations were evaluated in the Phase III clinical trials in addition to multiple bioequivalence studies. (b) (4)

Formulation A (the original formulation) was used in Studies 303 and 3307. Formulation B was used in Studies 305 and 306. Study 304 (a 1–year study with a 1-year extension phase) used both Formulation B and Formulation C.

Table 2: Formulations used in Pivotal Phase III Studies

A	B	C	D (TBM)
2 year Phase III Study # 303-US/EU/BR Endometrial safety, BMD, VVA, and VMS	2 year Phase III 304-WW Endometrial and BMD	2 year Phase III, 304-WW Endometrial and BMD Form: C used in the last 8 months of the first year and all of the second year	Used only in the following BE Studies: 1122, 1139, 1137 and 1142
Study # 3307 Endometrial safety and osteoporosis prevention	Study #305 3-months VVS Study 306 3-months VVA		

Source: Clinical Pharmacology reviewer

In study 304, Formulation B was administered initially, followed by a switch to Formulation C (b) (4) The study was extended to 24 months to obtain additional long-term efficacy and safety data to further support BZA/CE. Per the sponsor, the decision was not based on any efficacy or safety data, but rather feedback obtained from global experts (IND 62,288 (b) (4) pre-NDA meeting July 18, 2007). Later, data from BE Study 1117 showed BZA bioavailability of 18% lower than Formulation A. (b) (4) Other data presented by the sponsor showed that Formulation C provided mean BZA Cmax values ranging from 16% to 32% lower and mean BZA AUC values ranging from 22% to 36% lower compared to Formulation A. Study 3307, which used Formulation A, replaced Study 304 as a pivotal study.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission had several quality and integrity issues. The roadmap for formulation development continues to be inadequate and incomplete. Several clarifying submissions have been requested. The adverse event coding used different versions of MedDRA and data had to be recoded and resubmitted. Some endometrial biopsy data were not in the database and were added at a later date. The financial disclosure amounts were extreme (in excess of $625,000) for many investigators. Financial disclosure data were unavailable for 30% of primary investigators.

3.2 Compliance with Good Clinical Practices

The sponsor states that all studies (303, 304, 305, 306, and 3307) were designed and performed according to the guidelines for Good Clinical Practice, however, several issues were identified during the review.

For Study 303:
An internal audit showed critical GCP violations at site 326 that resulted in the termination of that site which accounted for fifteen dosed-subjects. The sponsor states that removal of those subjects did not alter the results obtained when these data were included in the analyses.

Reviewer's comments: Notification of the critical violations at site 326 were previously submitted on March 29, 2004 (IND 62288, SN-153) stating that site 326's participation in study 303 had ended. No additional information was provided. The site enrolled 17 subjects and was located in Pittsburgh, Pennsylvania (PI was Dr, Joseph Sanfilippo).

Findings, identified after the study closed, led to follow monitoring of safety data for all subjects at the South American sites, 447 and 450. When source documents were reviewed, no additional SAEs or AEs of special interest were identified. Due to the issues reported in 447 and 450, third party audits were performed at 24 (21%) additional sites -301, 310, 311, 312, 316, 336, 338, 361, 364, 373, 374, 392, 393, 400, 407, 415, 420, 421, 422, 424, 439, 440, 447, and 450. Most of the sites chosen were US sites with 7 foreign sites among them. A total of 128 subjects at 3 sites (447, 450 and 316) had missing or incomplete source documentation. The sponsor confirmed that the documentation was available during earlier evaluation.

For some patients, endometrial biopsy data were not in the clinical database. Some endometrial biopsies were available on endometrial biopsy worksheets at the Sponsor but had not been received from clinical study sites on CRFs and, as a result, were not available in the clinical database. In addition, slides and blocks from unscheduled biopsies for some subjects were identified for which there were no data on the database. The study database was reopened and the biopsy data from the hardcopy worksheets was added to the clinical database. In addition, slides with no available worksheets were sent to independent pathologists for evaluation, with results from these evaluations were also added to the database. The sponsor states the overall results and/or conclusions of the study were not affected by this process.

Mammograms for site 447 (76 subjects) and 450 (35 subjects) were lost in transit due to customs detainment. Source documentation was destroyed for Sites 343 (12 subjects) and 360 (56 subjects) due to clerical error.

Missing source documentation was identified in multiple studies: 286 (8.1%) subjects in Study 303, 5 (1.5%) subjects in Study 305, and 53 (8%) subjects in Study 306 and

8(0.7%) subjects in Study 304. [redacted] (b) (4)

3.3 Financial Disclosures

For NDA 22-247, there were 13 covered studies included in the bazedoxifene/ conjugated Estrogens (BZA/CE) product application.

The financial disclosure information provided in this NDA covers the time period from the start of the study through the end of the study plus one year. For all studies completed prior to the Pfizer-Wyeth merger (October 15, 2009), all financial disclosure activities were completed by Legacy Wyeth and reported in accordance to Legacy Wyeth SOPs or Pfizer. See Appendix 9.5 for listings of covered studies.

The applicant stated that these covered studies were not funded via variable compensation and none of the investigators in the study held any form of propriety interest in the product.

According to the Applicant, 113 investigators that participated in the covered studies had financial information to disclose. (Note: Investigators may have been counted more than once if they participated in more than one study). Of the investigators listed on the US FDA Form 3455, 105 investigators had significant payments of other sorts to disclose and 8 investigators had equity in the sponsor to disclose. All Investigator Initiated Research Grants associated with the investigators were paid directly to the Institution rather than to the individual investigator.

Significant payments of other sorts are listed in Appendix 9.5 by study protocol number with the name of the investigator and the total amount. (Note: In many cases, the listed investigator was not the primary investigator and the subjects enrolled represent the total enrolled for the site and not the number enrolled for the subinvestigator).

Reviewer's comment: Of the total 215 investigators (believed to be limited to primary investigators), 105 investigators had disclosable financial interests/arrangements. The Applicant has adequately disclosed the financial interests/arrangements of the investigators and appears to have demonstrated due diligence in trying to obtain the missing information. The financial disclosure amounts for studies evaluating the combination of bazedoxifene and conjugated estrogen range from $26,000 to $626,000. These amounts are much higher than what is generally seen in NDAs submitted to the Agency. The majority of the investigators with disclosed financial interests in excess of $25,000 were [redacted] (b) (4) **he sponsor states "the investigators were not involved in the analyses of these studies and/or efficacy data obtained from the patients and are not anticipated to benefit directly from the sale of the drug**

product." In this reviewer's opinion, based on the amount of financial compensation, it is reasonable to assume some bias may have occurred and the data may have been compromised intentionally or unintentionally at the patient level. However, since the main endpoints, endometrial biopsies and BMD, were read centrally and vasomotor symptom data were recorded on patient diary cards, the results were objective and the individual effect on the subject level data is anticipated to be small. In addition, for most of the larger financial disclosure amounts, the investigator accounted for (b) (6) the enrolled population (b) (6)

Based on the information above, the financial disclosure information appears not to affect the approvability of the application. See Clinical Investigator Financial Disclosure Form, Appendix 9.5, for further details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewer has identified the following review issues and is not recommending approval unless the issues are satisfactorily resolved.

This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product:

- A specification for (b) (4) BZA in the drug product needs to be included to address the impact (b) (4) on the safety and efficacy of the drug product. The applicant agreed to set a specification, which would be submitted on 04-Jun-2013. Until the proposed specification is submitted, reviewed and found acceptable, this remains an outstanding issue.
- The applicant needs to address the (b) (4) phenomenon discovered during the drug product manufacturing site inspection and the Method Validation performed at the St. Louis laboratory.

The Office of Compliance has not made the final recommendation for the facilities involved in this application.

Environmental Assessment has not been adequately prepared.

4.2 Clinical Microbiology

No Clinical Microbiology review was conducted for the NDA application.

4.3 Preclinical Pharmacology/Toxicology

Per the nonclinical reviewer, nonclinical data support approval of the combination of conjugated estrogens (CE; 0.45 or 0.625 daily dosage) plus bazedoxifene (BZA; 20 mg daily dosage), for treatment of osteoporosis, vasomotor symptoms (VMS), and vulvovaginal atrophy (VVA) in postmenopausal women. Nonclinical evaluation of the combination product was limited to pivotal repeat-dose toxicology studies and additional mechanistic and efficacy pharmacology studies. No new nonclinical safety concerns were identified. From a PharmTox perspective, the application is approvable.

4.4 Clinical Pharmacology

(b) (4)

The sponsor has not adequately demonstrated bridging amongst the formulations used in the clinical program to the final to-be-marketed formulation. This is a significant concern.

A safety concern involves the use of Formulation C (b) (4)

The therapeutic index window for BZA/CE for endometrial hyperplasia may be narrow at the high dose of CE (b) (4) In this regard, subjects with significantly higher clearance to BZA due to intrinsic or extrinsic factors may be at risk of underexposure and more likely to develop hyperplasia.

4.4.1 Mechanism of Action

The sponsor has paired conjugated estrogen with bazedoxifene. Conjugated estrogen and bazedoxifene function by binding to and activating estrogen receptors (ER) α and β, which vary in proportion from tissue to tissue. Conjugated estrogens are composed of multiple estrogens and are agonists of ER- α and β. Bazedoxifene is an estrogen agonist/antagonist that acts as an agonist is some estrogen-sensitive tissues and an antagonist in others. The combination of conjugated estrogen and bazedoxifene produces a mixed effect that is specific to the target tissue.

Conjugated estrogen combined with bazedoxifene has net estrogen agonist activity in bone. In the uterus, bazedoxifene appears to act as an estrogen antagonist and opposes the effect of CE conjugated estrogen. While the mechanism is not known, bazedoxifene appears to attenuate the effect of conjugated estrogen at target organs.

4.4.2 Pharmacodynamics

From the BZA monotherapy program, BZA has an effect on lumbar spine BMD and the effect on BMD appears to be dose dependent over 10, 20, and 40 mg daily doses over 24 month treatment compared to placebo. However, no concentration-relationship with BMD nor VTE exist. Pharmacodynamic data for the combination product was not performed by the sponsor.

4.4.3 Pharmacokinetics

The PK parameters following administration of BZA 20/CE 0.45 are shown in Table 3. For the combination product, the exposure (Cmax and AUC) was about twice higher after 10 days of multiple doses of BZA 20mg/CE 0.45 mg compared to single doses.

Table 3: PK Parameters for BZA on Day 1 and Day 10 following multiple dose administration of BZA 20/CE 0.45 (Study 1138-US)

Treatment		C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	AUC_{0-24h} (ng·h/mL)	R
Day 1 (single-dose)	Mean ± SD	4.62 ± 2.01	1.4 ± 0.7		36.1 ± 14.7	
	%CV	43.5	54.1		40.8	
	N	24	24		24	
	Geometric Mean	4.15	1.2		32.6	
	(Range)	(1.00-9.54)	(0.75-3.0)		(10.7-66.7)	
Day 10 (steady-state)	Mean ± SD	6.93 ± 3.87	2.5 ± 2.1	1.76 ± 1.05	70.8 ± 34.2	2.06 ± 0.65
	%CV	55.8	84.4	59.9	48.4	31.5
	N	24	24	24	24	24
	Geometric Mean	6.01	1.8	1.52	64.0	1.96
	(Range)	(2.43-18.1)	(0.75-6.0)	(0.56-4.15)	(33.2-152)	(1.03-3.16)

Source: Clinical pharmacology review

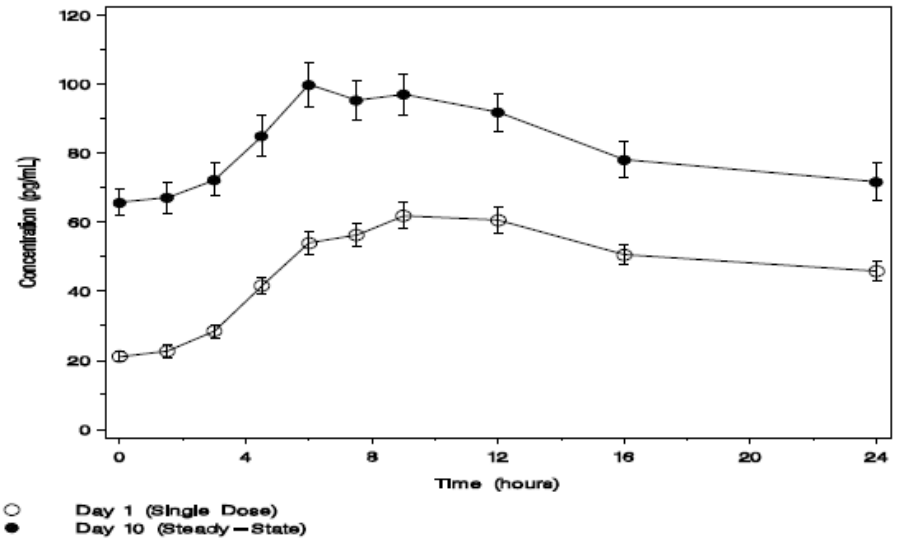
Furthermore, the exposure of CE components was also increased by approximately two times on Day 10 compared to Day 1 in the same study. Table 4 and Figure 2 show the exposure and the PK parameters of estrone as an example of CE component of CE Day 1 and Day 10, respectively. The same trend was also observed for all other CE components in this study.

Table 4: PK Parameters and Plasma Concentration-Time Profiles for unconjugated Estrone following multiple dose administration of BZA 20/CE 0.45 (Study 1138-US)

Treatment		C_{max} (pg/mL)	t_{max} (h)	C_{min} (pg/mL)	AUC_{0-24h} (pg·h/mL)	R
Day 1 (single-dose)	Mean ± SD	66.9 ± 19.5	10.4 ± 3.6		1156 ± 302	
	%CV	29.1	34.9		26.2	
	N	24	24		24	
	Geometric Mean	64.4	9.9		1120	
	(Range)	(36.1-114)	(6.0-24.0)		(644-1969)	
Day 10 (steady-state)	Mean ± SD	110 ± 32.3	7.4 ± 4.3	61.6 ± 19.1	1970 ± 569	1.72 ± 0.36
	%CV	29.4	58.4	31.0	28.9	21.1
	N	24	24	24	24	24
	Geometric Mean	105	6.6	58.3	1880	1.68
	(Range)	(45.2-166)	(1.5-24.0)	(25.4-98.2)	(803-3034)	(0.84-2.51)

Source: Clinical pharmacology review

Figure 2: Plasma concentration-Time Profiles of Unconjugated Estrone Following the Administration of 20/0.45 mg BZA/CE (Study 1138-US)



Source: Clinical pharmacology review

It can be concluded that from both monotherapy and combination programs the BZA exposure following BZA 20/CE 0.45 is consistently twice after multiple doses compared to single dose. Only single dose PK data is available for BZA 20 mg/CE 0.625 mg tablet. Table 5 shows the PK data for BZA 20 mg/CE 0.625 mg tablet (Formulation A) used in Phase 3 Studies 303 and 3307. PK data for unconjugated estrone are shown in Table 6.

Table 5: Plasma parameters for BZA following a single dose of BZA 20 mg/CE 0.625 mg tablet (Study 1122-US).

(b) (4)

Table 6: Plasma parameters for unconjugated estrone following a single dose of BZA 20/CE 0.625 mg BZA/CE tablet (Study 1122-US).

(b) (4)

BZA/CE will be administered without regard of food. However, food appeared to have modest effect on BZA pharmacokinetics. Following a high fat meal, Cmax was reduced (4.25 to 4.12 ng/ml) and BZA was slightly increased. (43.7 to 53.0 ng*h/mL)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant completed one Phase 2 dose-finding study (203) and four pivotal Phase 3 trials (303, 305, 306, and 3307) for registration of the following indications: treatment of moderate to severe vulvar and vaginal atrophy (VVA), treatment of moderate to severe vasomotor symptoms (VMS), and the prevention of postmenopausal osteoporosis. Additional studies included a Phase 3 study (304), an ancillary breast safety study (study 4000), and BZA monotherapy in the osteoporosis prevention (study 300) and osteoporosis treatment (study 301) populations. A tabular listing of studies is shown in Table 7. The bazedoxifene monotherapy Phase 3 studies are listed in Table 8, All studies were performed in healthy postmenopausal women with an intact uterus.

Table 7: Table of Studies –Pivotal and Supportive

Study number	Treatment Groups	Indication		
		VMS	VVA	PMO Prevention
Pivotal Phase 3				
303 2-yr **Endometrial Safety**	BZA 10 mg/CE 0.45 mg BZA 20 mg/CE 0.45 mg BZA 40 mg/CE 0.45 mg BZA 10 mg/CE 0 625 mg BZA 20 mg/CE 0.625 mg BZA 40 mg/CE 0.625 mg Raloxifene 60 mg Placebo	X	X	X
305 12-week	BZA 20 mg/CE 0.45 mg BZA 20 mg/CE 0.625 mg Placebo	X		
306 12-week	BZA 20 mg/CE 0.45 mg BZA 20 mg/CE 0.625 mg BZA 20 mg Placebo		X	
3307 1 yr **Endometrial Safety** **Breast density**	BZA 20 mg/CE 0.45 mg BZA 20 mg/CE 0.624 mg CE 0.45 mg/MPA 1.5 mg BZA 20 mg Placebo			X
Supportive Studies				
304 1yr study (+ 1yr EXT)	BZA 20 mg/CE 0.45 mg BZA 20 mg/CE 0.625 mg CE 0.45 mg/MPA 1.5 mg Placebo			X
4000 (ancillary study of 303) Breast density	BZA 20 mg/CE 0.45 mg BZA 20 mg/CE 0.625 mg Raloxifene 60 mg Placebo			
Phase 2 Studies				
203 **84 days** Endometrial safety	BZA 5 mg + CE 0.3 mg BZA 10 mg + CE 0.3 mg BZA 20 mg + CE 0.3 mg BZA 5 mg + CE 0.625 mg BZA 10 mg + CE 0.625 mg BZA 20 mg + CE 0.625 mg CE 0 .3 mg CE 0.625 mg BZA 5 mg CE 0.625 mg/MPA 2.5 mg Placebo			

Table 8: Bazedoxifene Monotherapy Studies

Monotherapy Studies				
300-GL 2-year	BZA 10 BZA 20 BZA 40 Raloxifene PBO			Prevention of PMO
301-WW 3 year	BZA 20 BZA 40 Raloxifene PBO			Treatment of PMO
PMO= postmenopausal osteoporosis				

5.2 Review Strategy

The available clinical data for Studies 303, 305, 306, 3307 and safety results from 304, provide the basis for consideration regarding the safety and efficacy of conjugated estrogen 0.625 mg and 0.45 in combination with bazedoxifene 20 mg for the treatment of moderate to severe vulvar and vaginal atrophy (VVA), treatment of moderate to severe vasomotor symptoms (VMS), and the prevention of postmenopausal osteoporosis. Efficacy from Study 304 will not be utilized due to the formulation issues and decreased bioavailability in that study.

The bazedoxifene monotherapy Phase 3 studies are denoted 300 and 301. (b) (4) From what is known, BZA and conjugated estrogen do not have a synergistic effect on the target organs. In fact, BZA appears to decrease or attenuates the effect of estrogen on bone, vasomotor symptoms and vulvar and vaginal atrophy. (b) (4)

5.3 Discussion of Individual Studies/Clinical Trials

The section contains synopses of the individual Phase 2 and Phase 3 studies.

Phase 2 Trial 203

3068A1-203-EU (referred hereafter as 203), was an 84-day, randomized, dose finding study in healthy postmenopausal women. The trial enrolled 414 healthy, postmenopausal women (age 40 to 65) with an intact uterus who were at least 1 year and < 10 years post menopausal, with an average of 4 hot flushes per day. Treatment groups and double dummy blinding scheme are listed in Table 9.

Table 9: Treatment Arms and Double Dummy Blinding Scheme

Treatment arm	N	Double Dummy Scheme		
		Bazedoxifene	Estrogen	Premarin/Provera
BZA 5mg	39	TSE-424 5mg	Placebo	Placebo
BZA 5mg/Prem 0.3	37		Premarin 0.3	
BZA 5mg/Prem 0.625	36		Premarin 0.625	
BZA 10mg/Prem 0.3	39	TSE-424 10mg	Premarin 0.3	Placebo
BZA 10mg/Prem 0.625	38		Premarin 0.625	
BZA 20mg/Prem 0.3	39	TSE-424 20mg	Premarin 0.3	Placebo
BZA 20mg/Prem 0.625	35		Premarin 0.625	
Prem 0.3	38	Placebo	Premarin 0.3	Placebo
Prem 0.625	36		Premarin 0.625	
Premarin 0.625/Provera 2.5	38	Placebo	Placebo	Prem/Pro
Placebo	37	Placebo	Placebo	Placebo

Source: Compiled from CSR

Assessments included: Baseline medical history, mammogram, pap smear, breast exam and gyn exam; Transvaginal ultrasound and endometrial biopsies obtained at screening, Day 28, and Day 84; Urine and serum bone markers: urine N-telopeptide, urine deoxypyridinoline, urinary CTx, serum osteocalcin, serum bone specific alkaline phosphatase, serum CTx) obtained at screening, baseline, Day 28 and Day 84; Lipids, coagulation profile (PT/PTT, fibrinogen, plasminogen activator inhibitor I activity and antigen, antithrombin II activity and antigen levels), homocysteine obtained at baseline, Day 28 and Day 84; Routine labs obtained during screening, Day 28 and Day 84; and Diary cards.

Efficacy endpoints were endometrial thickness by TVUS (primary) and endometrial biopsy (secondary). Other endpoints were estrogen effect, vaginal maturation, hot flushes, and bone turnover markers.

Safety endpoints included vital signs (including body weight, blood pressure, and heart rate), gynecologic and breast examinations, and laboratory determinations (hematology, blood chemistry and dipstick urinalysis) and other safety measurements, i.e., TVUS of ovaries (ovarian volume and ovarian cysts), vaginal bleeding, and breast tenderness.

Statistical Considerations: Handling of Missing data for all endpoints were reviewed. No imputations were made a screening. The on-treatment period for Bleeding/Spotting was as followed: No imputations were made if no test article record was available for that day. If the test article was taken for the day and all other diary card data were missing, then N (no spotting/bleeding) was assigned. If the test article was not taken and all diary data were missing then the diary card was assigned a code of B (bleeding) for data on bleeding and S (spotting) for data on spotting.

Reviewer's comment: The handling of missing data for bleeding/spotting seems arbitrary and seems to favor reports of bleeding/spotting/breast tenderness if no test article was taken and favors no AEs if test article was taken. A copy of the diary card was not included. In comparison, in the Phase 3 study (303) missing

data was to remain as missing in the screening period as well as on-therapy period.

Protocol Violations - There were a total of 7 subjects who were discontinued due to a protocol violation and no imbalances were seen between groups. There were 3 randomized patients who did not meet the inclusion and exclusion criteria: patients 203008-506 and 203009-546 in the BZA 10 mg/Premarin 0.3 mg group, and patient 203015-0827 in the BZA 10 mg/Premarin 0.625 mg group. The first 2 patients did not receive any test article, the last one did receive test article and her protocol deviation was considered as minor.

Concomitant Medications - The use of estrogen-, progestin-, or androgen-containing medications (within 8 weeks); SERMs other than the test article (within 8 weeks); lipid-lowering agents; anticoagulants; chronic use (longer than 10 days) of corticosteroids, except inhaled; belladonna alkaloids; ergotamine tartrate; phenobarbitone or other medications that may affect vasomotor symptoms; non-prescription remedies for treatment of vasomotor symptoms (ie, soy, black cohosh, dong quai, etc) were prohibited.

Disposition- Of the 408 subjects in the safety population,26 (6%) of patients discontinued mainly due to adverse events 13 (3%).

Demographics - The mean age of subjects was 52-54 years with 92-100% of Caucasian race. Patients were recruited from 22 centers: 11 centers in Czech Republic (152 patients), 6 centers in The Netherlands (111 patients), 2 centers in Denmark (67 patients), 2 centers in France (60 patients) and 1 center in Germany (22 patients). There were no statistically significant differences across groups based on baseline characteristics.

Efficacy- Trial 203

- Primary Efficacy: Endometrial Thickness
  The 20 mg BZA dose was the most effective in preventing endometrial stimulation in combination with 0.3 mg Premarin. The ANCOVA mean change of Premarin 0.625 and 0.3 was 5.5 mm and 3.92 mm, respectively. BZA 20/Prem 0.625 and BZA 20/Prem 0.45 showed mean changes of 3.54 and 2.94 (ITT population), respectively. The placebo value was 2.95. Pairwise comparisons of endometrial thickness showed a -1.95 mm change in the BZA 20/Prem 0.625 group ($p<0.001$) vs Prem 0.625 and -0.98 in the BZA 20/Prem 0.3 group vs Prem 0.3.

- Hot Flushes – Weekly
  The average number of HFs at baseline was approximately 6-7 per day with a range of 42.9 to 55.3 HFs per week. The number of HFs per week decreased over

each 4-week period. The pairwise comparison for BZA 20/Prem 0.625 and BZA 20/Prem 0.3 vs placebo was -13.24 and -3.48, respectively (Table 10).

Table 10: Hot Flushes per Week at Weeks 9-12: Pairwise comparison – ITT

Treatment group	vs. Comparator	Estimate	SE	95% CI	p-value
BZA 20/Prem 0.625	Placebo	-13.24	3.40	(-19.91, -6.56)	<0.001
BZA 10/Prem 0.625	Placebo	-12.95	3.39	(19.62, -6.28)	<0.001
BZA 5/Prem 0.625	Placebo	-15.05	3.37	(-21.67, -8.42)	<0.001
BZA 20/Prem 0.3	Placebo	-3.48	3.33	(10.03, 3.07)	0.297
BZA 10/Prem 0.3	Placebo	-6.33	3.37	(-12.97, 0.30)	0.061
BZA 5/Prem 0.3	Placebo	-13.03	3.39	(-19.72, -6.37)	<0.001
Prem 0.625/MPA 2.5	Placebo	-18.75	3.44	(-25.52, -11.98)	<0.001
Source: Adapted from Table 9.4.5.1-2, p.81					

Based on data at Weeks 9 to 12 compared to baseline, BZA (5, 10 and 20) groups combined with Prem 0.625 showed efficacy in decreasing the number of HFs per week. BZA in combination with Premarin 0.3 showed less efficacy. The 0.3 Prem dose with 10 or 20 BZA did not provide good efficacy in decreasing the number of hot flushes. The number of hot flushes at Week 4 and Week 12 will be needed to support hot flush efficacy in Phase 3.

- Hot Flushes - Total Severity Score

The adjusted total severity score calculation for each 4-week period was: [(Number of mild HFs x 1) + (Number of moderate HFs x 2) + (Number of severe HFs x 3) x 28]/Number of days of diary data per 4 weeks. Pairwise comparisons are shown in Table 11.

Reviewer's comment: All BZA combination arms had lower mean severity scores at Weeks 9 to 12 compared to placebo. The greatest efficacy (lowest scores) were seen in Prem 0.625/MPA, Prem 0.625, and BZA 5/Prem 0.625 groups.

Table 11: Total Severity Score at Weeks 9 To 12: Pairwise Comparisons – ITT

Treatment group	vs. Comparator	Estimate	SE	95% CI	p-value
BZA 20/Prem 0.625	Placebo	-83.57	24.98	-132.68, -34.45	<0.001
BZA 10/Prem 0.625	Placebo	-84.32	24.95	-133.38, -35.25	<0.001
BZA 5/Prem 0.625	Placebo	-102.67	24.77	-151.38, -53.96	<0.001
BZA 20/Prem 0.3	Placebo	-30.73	24.50	-78.92, 17.45	0.211
BZA 10/Prem 0.3	Placebo	-48.69	24.81	-97.48, 0.10	0.050
BZA 5/Prem 0.3	Placebo	-88.51	24.97	-137.61, -39.42	<0.001
Prem 0.625/MPA 2.5	Placebo	-120.60	25.32	-170.39, -70.80	<0.001
Source: Adapted from Table 9.4.5.2-2					

- Bone Turnover Markers

  All BZA/Prem treatment groups showed a decrease in serum CTx (-21 to -38%, median values), suggesting efficacy in decreasing bone turnover. The magnitude of osteocalcin decrease correlated with increasing BZA dose for both Prem 0.3 and 0.625. Smaller changes in osteocalcin were seen with the Prem 0.625 compared to Prem 0.3, however no trends were seen.

- Coagulation parameters

  The Prothrombin time (PT) mean values at day 84 were between 0.97 and 1.12 for each of the treatment groups. The median percent change from baseline ranged from -9.7 to 0%. There appears to be more PT shortening occurring with BZA 20 (combined with either 0.3 or 0.625 CE) compared to lower BZA (5 or 10 mg) doses. This finding may explain a hypercoagulable state however the Premarin 0.625 only data in this trial do not correlate and confirm this trend. When compared to placebo, no statistical significance was seen in the BZA/Prem dose groups. All groups showed a decrease in PTT mean and median change. No dose response was seen for fibrinogen, plasminogen activator inhibitor-1, antithrombin III, or homocysteine.

Safety – Trial 203

Overall, 73% of subjects overall reported one or more adverse event while on treatment. The most common (>10%) AEs in all groups were headache, infection and flu syndrome. No deaths occurred during the study. Seven serious adverse events occurred during the study and no imbalance was seen between groups. There was one inconclusive chest pain event. No VTEs were reported. The incidence of bleeding in the Premarin 0.3 (5.1%) or 0.625 (2.9%) were similar to placebo (5.4%) compared to a higher rate in the Premarin/MPA group (35.1%).

Conclusion:

There was adequate dose-finding for bazedoxifene in the Phase 2 study. The BZA 20 mg dose was the lowest dose that provided sufficient endometrial protection. For VMS, the Phase 2 study showed that CE 0.3 was insufficient to provide enough vasomotor or

(b) (4) efficacy in combination with BZA 20 mg. BZA 20 mg in combination with Premarin 0.3 or 0.625 was well-tolerated.

Phase 3 Trial 303

3115A1-303-US/EU/BR (referred hereafter as 303) was a 24-month, randomized, multicenter (94 sites), placebo-and active-controlled study. The study randomized 3544 healthy postmenopausal women (age 40-75) with an intact uterus and acceptable baseline endometrial biopsy results into 8 treatment groups.

Table 12: Dose groups – Trial 303

Group	Treatment	N (target)
1	CE 0.625/BZA 10	(b) (4)
2	CE 0.625/BZA 20	
3	CE 0.625/BZA 40	
4	CE 0.45/BZA 10	375
5	CE 0.45/BZA 20	375
6	CE 0.45/BZA 40	375
7	Raloxifene 60 mg	375
8	Placebo	375

Each study site enrolled subjects into the Main Study, the Osteoporosis Prevention I Substudy or the Osteoporosis Prevention II and Metabolic Substudy. Each of these substudies were further divided by the presence or absence of transvaginal ultrasound (TVUS) assessment resulting in six study groups (A, B, C, D, E or F). Each site was to enroll the same number of subjects (n=32 subjects).

Table 13: Study Design – Trial 303

Study Group	Description	# of Sites	Subjects per Site	# of Subjects
A	Main Study Without TVUS	19	32	608
B	Main Study With TVUS	10	32	320
	(Subtotal - Main Study)	(29)		(928)
C	Osteoporosis Prevention I Substudy Without TVUS (>5 years postmenopausal)	27	32	864
D	Osteoporosis Prevention I Substudy With TVUS (>5 years postmenopausal)	13	32	416
	(Subtotal - Osteoporosis Prevention I Substudy)	(40)		(1280)
E	Osteoporosis Prevention II and Metabolic Substudy Without TVUS (≥1 year and ≤5 years postmenopausal)	16	32	512
F	Osteoporosis Prevention II and Metabolic Substudy With TVUS (≥1 year and ≤5 years postmenopausal)	9	32	288
	(Subtotal - Osteoporosis Prevention II and Metabolic Substudy)	(25)		(800)
	Total Study	94		3008

The sponsor prospectively enrolled subjects in the Osteoporosis Prevention I Substudy based on menopausal status: at least 5 years postmenopausal and a BMD T-score at the lumbar spine or total hip between –1 and –2.5 (inclusive), and at least 1 additional risk factor for osteoporosis. The sponsor prospectively enrolled subjects into Osteoporosis Substudy II based on menopausal status: < 5 years and at least one osteoporosis risk factor (one risk factor could be T-score between -2.5 and -1). Medical Officer Review of the study protocol dated October 9, 2001, stated the "inclusion and exclusion criteria, both general and specific to the sub-studies, were reviewed and were acceptable with the following exceptions" none of which dealt with inclusion of only osteopenic subjects. Approved applications for estrogen and non-estrogen products for the prevention of PMO have enrolled subjects with normal BMD at baseline. Approximately, 55% of subjects in the Substudy II were osteopenic by T-score. BMD results in this population will also be presented as their fracture risk, change in BMD, and risk/benefit profile may be differ from their non-osteopenic counterparts. Subjects in the Osteoporosis Substudies had daily calcium and vitamin D assessed at baseline and were supplemented with Caltrate 600 + D if calcium intake was <1000 mg.

Key inclusion/exclusion criteria are:

Inclusion Criteria

- Healthy postmenopausal women, 40 to 75 years, with intact uterus
- Serum FSH >30 mIU/mL and serum 17β-estradiol concentration <183.5 pmol/L (50 pg/mL) at screening.
- Acceptable endometrial biopsy report at screening either: proliferative endometrium; weakly proliferative endometrium; secretory endometrium; endometrial tissue, other

(including benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc.)
- Last natural menstrual cycle at least 12 consecutive months before screening.
- BMI less than or equal to 32.2 kg/m2
- For subjects in the Osteoporosis substudies, the lumbar spine scans at screening must differ by less than 5% and the total hip scans at screening must differ by less than 7.5% at baseline.
- For Osteoporosis Prevention I Substudy: Subjects must be more than 5 years postmenopausal and have a bone mineral density (BMD) T-score at lumbar spine or total hip ≤ -1 and ≥ -2.5 and have at least one of the following risk factors: Family history of osteoporosis, Early menopause (occurring at or before the age of 40), Current history of smoking, Past history of excessive alcohol use, Diet low in calcium, Inactive lifestyle, Thin and/or small frame (weight < 50 kg and/or BMI < 18 kg/m2), Caucasian or Asian
- For Osteoporosis Prevention II and Metabolic Substudy: Subjects must be at least 1 year but no more than 5 years postmenopausal and have at least one of the following risk factors: BMD T-score at lumbar spine or total hip ≤ -1 and ≥ -2.5, Family history of osteoporosis, Early menopause (occurring at or before the age of 40), Current history of smoking, Past history of excessive alcohol use, Diet low in calcium, Inactive lifestyle, Thin and/or small frame (weight < 50 kg and/or BMI < 18 kg/m2), Caucasian or Asian

Exclusion Criteria

A history of:

- Known or suspected estrogen-dependent neoplasia
- Endometrial hyperplasia;
- Malignancy within the previous 10 years, except basal cell carcinoma of the skin
- Thrombophlebitis, thrombosis or thromboembolic disorders
- Cerebrovascular accident, stroke, or transient ischemic attack
- Neuro-ocular disorders, eg, retinal vasculitis
- Myocardial infarction or ischemic heart disease
- Chronic renal or hepatic disease
- Gallbladder disease (subjects who have had a cholecystectomy may be enrolled)
- Use of any oral estrogen-, progestin-, androgen-, or SERM-containing medications without washout.
- For the Osteoporosis Prevention Substudies: History of osteoporotic fracture; Use of glucocorticosteroids, calcitonin, anabolic steroids or parathyroid hormones, therapeutic fluoride, bisphosphonates, anticoagulants or prescription lipid-lowering agents without washout.

Active presence of:

- Unresolved abnormal mammogram or pap smear

- Endocrine disease except for controlled hypothyroidism or diet controlled diabetes mellitus (for the Osteoporosis Substudy, subjects with diabetes mellitus are excluded)
- LFT elevation (>1.5 times the upper limit of normal)
- Elevated blood pressure (>160 /100)
- Known alcohol or drug abuse.

For Osteoporosis Substudies

- Diseases that may affect bone metabolism, eg, hypercalcemia, hypocalcemia, osteogenesis imperfecta, chronic gastrointestinal disease, or Paget's disease.
- Two (2) or more abnormal lumbar vertebrae
- Lumbar spine or total hip baseline BMD measurement T score exceeding 2.5 standard deviations below the mean for healthy young women

Efficacy endpoints Trial 303:
The primary endpoint was the incidence of endometrial hyperplasia after 1 year. Endometrial hyperplasia serves as a surrogate endpoint for endometrial cancer. Endometrial biopsies were performed at screening, and months 6, 12, and 24. At clinical sites also performing TVUs, if the ultrasound examination at month 12 or 24 identified non-measurable endometrium, endometrial double-walled thickness greater than 8 mm, or a focal abnormality, then hysteroscopy with directed biopsy was to be performed in place of a routine biopsy. Additional endometrial biopsies were to be performed for any subject who experienced prolonged or heavy uterine bleeding, or bleeding occurring more than 3 months since the last biopsy. All endometrial biopsy specimens were read centrally by 2 pathologists and classified as either "malignancy", "hyperplasia", or "not hyperplasia". Subjects could have been enrolled if they had "endometrial tissue insufficient for diagnosis", "no endometrium identified" or "no tissue identified."

As this study predates the estrogen and estrogen-progestin guidance it was acceptable to require only 2 blinded pathologists with a third pathologist included only if there was disagreement. The current guidelines require three independent pathologists throughout the study.

The main secondary endpoint was the mean percent change from baseline in BMD of the lumbar spine after 2 years of therapy. Other secondary endpoints are discussed below.

Table 14: Secondary Efficacy Parameters

Parameter	Measurement Method	Time Points[a] (Months)	Endpoints Analyzed
Endometrial hyperplasia	Endometrial biopsy	6, 12, 24	Incidence of endometrial hyperplasia Primary: at 12 months Secondary: at 6 months and 24 months
BMD of lumbar spine	DXA[b]	6, 12, 18, 24	BMD of lumbar spine Primary: mean percent change from baseline at month 24 Secondary: mean percent change from baseline at all time points; annual percent change (slope analysis); responder analysis (subjects with no change or increase in BMD from baseline to month 12 and 24)
BMD of hip (total hip, femoral neck, trochanter, intertrochanteric area)	DXA[b]	6, 12, 18, 24	BMD of hip Mean percent change from baseline at all time points; annual percent change (slope analysis)
DXA scan of distal radius (radius 33%, radius total, and radius UD)	DXA[b]	12,24	BMD of distal radius Mean percent change from baseline at each time point
Serum markers of bone metabolism (osteocalcin, C-telopeptide)[c]		6, 12, 18, 24	Serum concentrations Median percent change from baseline at months 6, 12, 18, and 24 for subjects who participated in the Metabolic Substudy
Height		12, 24	Percent change from baseline at months 12 and 24
Vaginal atrophy	Vaginal smear	6, 12, 18, 24	Change from baseline in the composition of the vaginal epithelium (% parabasal cells, % intermediate cells, % superficial cells) at months 6, 12, 18, and 24

a. All variables were measured at baseline; only post-baseline time points are shown here.
b. DXA = dual-energy x-ray absorptiometry; only for subjects in the Osteoporosis Prevention Substudies
c. Only for subjects participating in the metabolic substudy

Source: Table 6-5, p. 37 303 CSR

- Bone Mineral Density (BMD) was determined by DXA at the lumbar spine (L2-L4) and left hip at screening and months 6, 12, 18, and 24. Duplicate scans were done at screening, month 12 and month 24. For the LS, the scans had to differ by less than 5%. If not, the subject was to return for a third scan, and the 2 values closest to the mean of the 3 and within 5% of each other were reported. The hip scans had to differ by less than 7.5%, if not a third scan was performed and the 2 values closest to the mean of the 3 and within 7.5% of each other were reported. DXA of the distal radius (1/3, ultradistal, total radius) were obtained at screening and month 12 and 24 at selected study sites.
- Bone Turnover Markers: Serum osteocalcin and C-telopeptide were obtained at months 6, 12, 18, and 24 in the Metabolic Study (Osteoporosis Prevention Substudy II)
- (b) (4)

(b) (4)

- A daily diary collected information on hot flushes (number and severity), sexual activity/dyspareunia, sleep, breast pain and bleeding/spotting.
- Menopause-Specific Quality of Life Questionnaire (MENQOL): The MENQOL is a 27-item questionnaire that generates 4 domain scores for vasomotor, psychosocial, physical, and sexual and a total score. The MENQOL was administered at baseline and at months 3, 6, 12, 18, and 24

Safety endpoints Trial 303

The estrogen- and SERM- specific safety evaluations are shown below.

Table 15: Safety endpoints – Trial 303

Procedure	Variables Evaluated	Evaluation Time Points (Months)
Endometrial biopsy	Polyps (incidence) Proliferative endometrium (incidence)	(baseline, 6, 12, 24)
Transvaginal ultrasound (TVU)	Endometrial thickness Ovarian volume Ovarian cysts (number and size)	(baseline, 12, 24)
Metabolic Substudy determinations	Coagulation factors Carbohydrates and lipids Plasma homocysteine, C-reactive protein, TSH	(baseline, 12, 18, 24)
Breast exam and mammography	Annual safety monitoring	(baseline, 12, 24)

Source: Documentation of Statistical and Analytical Methods [16.1.9].

Additional safety assessments included standard safety measurements (adverse events, clinical laboratory safety, blood pressure, weight, and ECGs).

Reviewer's comment: It appears that fractures were captured as adverse events and were not adverse events of special interest.

Statistical Considerations Trial 303:
Sample size for the main study was based on endometrial hyperplasia endpoint at 1 year. Assuming at least 80% of those enrolled would be included in the hyperplasia analysis at 1 year, the pre-specified sample size enrollment was 375 per treatment group. For the Osteoporosis SubStudy II, sample size was based on mean percent change from baseline in BMD for LS and hip at 2 years. Assuming a standard deviation of 3.5 for the mean percent change from baseline in lumbar spine BMD, a sample size of 67 subjects per group would provide 90% power to detect a difference of 2.0% in the mean percent change between BZA/CE and placebo groups at the 0.048 level (significance level adjustment due to interim analysis). To account for smaller changes at the hip, the sample size was increased to 100 per group. For the Osteoporosis

SubStudy I, a larger sample size was needed due to smaller changes expected in older patients. Assuming a standard deviation of 3.5%, 117 subjects per group would be needed to provide 90% power to detect a difference of 1.5% at the 0.048 level. A sample size of 160 per group was chosen in order to provide 90% or greater power for both LS and TH.

Primary Efficacy Parameter: Incidence of Endometrial Hyperplasia
The primary endpoint was incidence of endometrial hyperplasia at 1 year using the Efficacy Evaluable (EE) population. The EE population was defined as subjects who had taken at least 1 dose, had screening endometrial biopsy, or had hyperplasia diagnosed prior to the time point. The MITT at 6 months and 2 years were also analyzed. The MITT was defined as all randomized subjects who took at least 1 dose and had screening and on-therapy data.

Bone Mineral Density (BMD)
BMD was analyzed separately for the Osteoporosis Subgroup I (using Lunar measurements) and Subgroup II (using Hologic measurements). The main efficacy endpoint was the mean percent change from baseline to month 24 between the BZA/CE groups and placebo using the MITT population and last observation carried forward (LOCF). Secondary analyses were done for a) all time points (only at the lumbar spine [LS[), b) the EE population, 3) the completer population and 4) hip sites (total hip, femoral neck, trochanter, intertrochanteric). A Responder Analysis was performed for the LS at Month 12 and Month 24.

The BMD MITT population included all subjects who took at least one dose and had baseline and at least one on-therapy BMD. The BMD EE population included subjects who met the MITT criteria and did not have substantial violations. The Completer population included subjects who met the BMD EE criteria and did not withdraw prematurely and had a 24 month BMD value.

ANCOVA was the main model for analysis and used treatment and center for factors and baseline BMD and years since menopause as covariate. To address multiplicity for the primary endpoint (LS BMD), a stepwise approach was used beginning with BZA 10/0.625, BZA 20/0.625, BZA 40/0.625, then the 0.45 dose regimens. The Osteoporosis II group was tested first. All comparisons were 2-sided at the 0.048 level (with adjustment for an interim analysis).

For the responder analysis (limited to lumbar spine data), a BMD responder was defined as a subject with no change or increase from baseline in LS BMD at months 12 or 24. Responder rates or percentage of responders at each time point were compared between BZA/CE groups and placebo using MITT.

DXA results of 1/3 radius, total radius and UD radius were analyzed using MITT population as primary.

Hot Flushes
To address multiplicity for the primary endpoint, a similar stepwise approach as used for BMD was used - beginning with BZA 10/0.625, BZA 20/0.625, BZA 40/0.625, then the 0.45 dose regimens. However, both the week 4 and week 12 had to show statistical significance before proceeding to the next group.

The analysis of change from baseline in severity was done using 2 different definitions for the average daily severity score for baseline. The first was stated in the SAP where only moderate and severe hot flushes were counted at baseline.

$$\frac{(\#\text{ moderate hot flushes}) \times 2 + (\#\text{ severe hot flushes}) \times 3}{\text{total \# of moderate and severe hot flushes on that day}}$$

The sponsor later adopted an alternative definition which included all baseline hot flushes (mild, moderate and severe) in the calculation of baseline average daily severity. This definition was used for the principal analyses by the sponsor.

Reviewer's comment: The inclusion of mild hot flushes into the baseline value used to assess change in moderate and severe HFs seems problematic. This change appears to inflate the baseline severity. This is further discussed in the efficacy section (6.1.4).

VVA:

(b) (4)

Protocol Violations:
Protocol deviations included inclusion/exclusion criteria violations, incorrect dose of test article taken, prohibited concomitant usage of medications, and hysteroscopy with directed endometrial biopsy not performed when required. A total of 1062 (31.3%) subjects had protocol deviations. Use of prohibited medications affecting lipids or coagulation occurred in 156 subjects (18.1%) in Substudy II, and use of prohibited medications affecting bone metabolism (including bisphosphonates, fluoride, NSAIDs, etc) occurred in 370 subjects (16%) in Substudies I and II combined. A total of 53

(1.6%) subjects were withdrawn due to protocol deviations. The sponsor excluded additional subjects from the EE population for the following reasons: no biopsy at screening or at Month 12, not postmenopausal, malignancy (for endometrial hyperplasia), no baseline BMD, no on-therapy BMD, postmenopausal status, noncompliance (for BMD, Substudy 1) (Table 16).

Table 16: Number of subjects excluded from EE due to protocol deviations

	Conjugated Estrogens 0.625 mg			Conjugated Estrogens 0.45 mg				
Protocol Deviation[a]	BZA 10 mg (b) (4)	BZA 20 mg	BZA 40 mg	BZA 10 mg N = 430	BZA 20 mg N = 433	BZA 40 mg N = 423	Raloxifene N = 423	Placebo N = 427
EE population - endometrial hyperplasia at month 12								
No valid screening biopsy	(b) (4)			0	0	0	0	2 (<1)
No month 12 biopsy or no hyperplasia before month 12				110 (26)	97 (22)	113 (27)	124 (29)	114 (27)
Not postmenopausal				0	0	1 (<1)	2 (<1)	2 (<1)
Diagnosis of malignancy				0	1 (<1)	0	0	1 (<1)
EE population - BMD lumbar spine (Substudy I)								
N (Groups C & D)	(b) (4)			186	182	176	188	184
Did not have a baseline BMD				1 (<1)	0	0	1 (<1)	0
Did not have ≥1 on-therapy BMD				20 (11)	24 (13)	19 (11)	28 (15)	28 (15)
Did not meet inclusion criterion #10[b]				7 (4)	1 (<1)	4 (2)	4 (2)	5 (3)
Did not meet inclusion criterion #5[c]				3 (2)	0	1 (<1)	0	0
Study medication compliance <80%				24 (13)	27 (15)	24 (14)	29 (15)	29 (16)

Source: Table 8-7, p. 91, CSR 303

Bone active medication taken by subjects during the study included chronic steroids, diuretics, calcitonin, thyroid replacement, therapeutic fluoride, bisphosphonates and NSAIDS. The incidence ranged from 14.6% to 19% (mean 16%) across treatment groups with the highest rates in the BZA 10/CE 0.45 and BZA 20/CE 0.625 groups. Three subjects were excluded from the trial based on prohibited medication, including intake of Fosamax, testosterone, and raloxifene. The sponsor states that these medications "in the context of the 2 year study are unlikely to have an impact on BMD". Based on available data submitted with the NDA (rate of bone active drugs of 16%), this reviewer does not agree with the sponsor's assessment. In Response to an Information Request submitted April 9, 2013, the sponsor provided summary data and accompanying datasets outlining the type and duration of concomitant therapy and BMD changes.

The sponsor confirmed that a total of 370 subjects took bone active medication during the study. The breakdown across treatment groups is shown in Table 17. The majority of the medication occurred during the on-study treatment period. There was an imbalance in numbers of patients taking concomitant bone active meds in the 0.625/20 and 0.45/20 dose groups

Table 17: Percentage of Subjects in Osteoporosis Subgroups I and II taking Bone Active Drugs

	CE/BZA dose				RLX	PBO	Total
	(b) (4)	0.45/10	0.45/20	0.45/40			
Prior to Study		1.4%	2.0%	4.6%	3.1%	1.7%	10.6%
During Study		18.3%	14.7%	15.8%	15.3%	15.1%	16%
Source: April 9, 2013 submission							

From review of the datasets, the most common medications were nonsteroidals, steroids (oral and nasal), Synthroid, and flaxseed oil. Two subjects received Fosamax – Subject 1 (303-338-302435) receiving CE 0.45/BZA 10 who had been on Fosamax chronically although the actual timing is unclear as the prohibited medication start date (9/1/2003) was later than the study termination date (8/15/2003). Subject 2 (303-418-307561) – who while receiving CE 0.45/BZA 40 started Fosamax on 11/3/2003 and continued the medication for 65 days until study termination on 2/2/2004.

Many of the concomitant medications had the potential to decrease BMD with only several medications leading to potential increases in BMD. As listings for testosterone and raloxifene were not located in the dataset, the reviewer estimates a total of at least 4 events involved co-administration of bisphosphonates, testosterone and raloxifene.

A total of 5.6% of subjects had protocol violations due to having had more than 1 endometrial biopsy during screening. This represents those subjects who had insufficient endometrium who needed a second biopsy or had to be excluded. The distribution was unbalanced between groups which ranged from 4.1 to 6.8%. It is unlikely that the magnitude of the imbalance significantly impacted the results.

Concomitant Medication:
A total of 16% of subjects in the osteoporosis substudies took prohibited bone active medications during the study (see above). Discussion of the BMD results comparing the MITT population and the population taking bone active drugs is presented in the efficacy section.

Phase 3 Trial 305

3115A1-305-US (referred to hereafter as 305) was a 12-week, multicenter, double-blind, 3 parallel group, placebo-controlled study. The study randomized 332 healthy postmenopausal women (age 40-65) with an intact uterus, who had also been seeking treatment for hot flushes and report at least 7 moderate to severe hot flushes per day or 50 per week. Subjects either had 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL. Subjects were randomly assigned to daily CE 0.625/BZA 20, CE 0.45/BZA 20 or placebo in 2:2:1 ratio.

Medications known to treat VMS were prohibited and required up to 8 weeks of washout. Certain non-hormonal moisturizers for relief of VVA symptoms were permitted. The exclusion criteria were similar to Study 303.

Efficacy endpoints Study 305:

The co-primary endpoints were the reduction in the average daily number of moderate and severe hot flushes and reduction in daily severity of hot flushes at Week 4 and Week 12 compared to placebo

- The average daily number of moderate and severe hot flushes for each week was calculated as follows:

$$\frac{\text{Sum of the number of moderate and severe hot flushes on each day}}{\text{Number of days with data}}$$

- The average daily severity of hot flushes for each week was calculated as follows:

$$\frac{\text{Sum of the daily severity scores}}{\text{Number of days with data}}$$

where the daily severity score was calculated as:

$$\frac{\text{(no. mild hot flushes) x 1 + (no. moderate hot flushes) x 2 + (no. severe hot flushes) x 3}}{\text{Total number of hot flushes}}$$

and a daily severity score of zero (0) was assigned if it was reported that no hot flushes occurred on that day.

Secondary efficacy endpoints related to VMS included:

- Responder analysis, with responders defined as subjects who reached at least a 50% or a 75% decrease from baseline in the number of hot flushes for moderate and severe hot flushes and for mild, moderate, and severe hot flushes.
- Reduction in the number of mild, moderate, and severe hot flushes.
- Reduction in the daily composite score, calculated as: number of mild hot flushes x 1 + number of moderate hot flushes x 2 + number of severe hot flushes x 3.
- Time to reach a 50% decrease from baseline in the number of hot flushes for at least 3 consecutive days.
- Examination of hot flushes by age subgroups.

Other secondary efficacy variables included results from the MOS sleep scale, MENQOL, and MS-TSQ and the presence of breast pain.

Reviewer's comment: These other secondary endpoints are exploratory and will not support labeling claims.

Safety endpoints Trial 305

Evaluation of AEs, clinical laboratory determinations, physical examinations (including breast and pelvic examinations), vital signs (including weight and blood pressure measurements), transvaginal ultrasound (TVU) findings, and endometrial histology

- Transvaginal Ultrasound: TVU was performed at baseline and Week 12
- Endometrial biopsy: Biopsies were performed at baseline. Repeat biopsies were performed at Week 12 (or at early withdrawal after at least 6 weeks) if TVU thickness exceeded 4 mm. Slides were prepared at (b) (4) Biopsies were read centrally by 2 primary pathologists. If they disagreed, a third pathologist was consulted.

Statistical Considerations Trial 305:

The sample size was based on the expected differences between the BZA/CE treatment groups and placebo in mean daily number and severity of hot flushes. A total of 104 subjects per group for the BZA/CE treatment groups and 52 subjects for the control group was to provide greater than 90% power to detect a difference of 3 hot flushes between a BZA/CE treatment group and placebo with a 0.05 two-sided significance level (standard deviation [SD] = 4.8). A difference between groups of 3 moderate-to-severe hot flushes per day was chosen as the basis for the sample size calculation because differences of this magnitude or greater have been observed in previous studies. Per the sponsor, this was not intended to represent the minimal clinically important difference, which is likely to be a smaller number. These same subject totals were to also provide greater than 90% power to detect a difference in mean severity score of 0.5 between a BZA/CE treatment group and placebo (assuming SD of 0.8). A total of 130 subjects in each BZA/CE treatment group and 65 subjects in each control group were to be enrolled to have allowed for up to 20% of the subjects being excluded from the analysis.

The MITT population, defined as those who had taken at least 1 dose, at least 5 days of data at baseline, and at least 5 days of data for at least 1 on-therapy week, was used with LOCF for the primary analysis at weeks 4 and 12. ANCOVA was used to compare BZA/CE groups and placebo with treatment, study site, and baseline value as covariates plus treatment by study site interaction. The primary ANCOVA analysis was also performed in the MITT and PP populations based on an observed case (OC) analysis.

Reviewer's comment: The MITT contained subjects who did not meet the entry criteria for the requisite number of HFs. The Per Protocol analysis excluded these subjects, in addition to including subjects who had at least 5 days data per week

(on-therapy phase) for the week to be evaluated; compliance ≥80%, were not taking unacceptable concomitant medications, any medication that could impact the assessment of the primary endpoints, or medications/ remedies known to treat VMS; had no major protocol violations and had a confirmed menopausal status.

Protocol Violations:

A total of 80 (25.2%) subjects had protocol deviations in the study. Of these, 74 subjects (23.3%) had protocol deviations occurring due to inclusion/exclusion violations and 28 (8.8%) had protocol deviations while on study drug. Imbalances were seen in the following categories: lack of FSH confirmation of postmenopausal status when amenorrhea was <1 year, subjects without the required number of HFs at baseline, inadequate TVU at baseline, and use of prohibited medications known to treat VMS during the study. Overall, there was even distribution of deviations across treatment groups. Subjects who were withdrawn from the study due to protocol violations were included in the MITT analysis with the exception of eight subjects due to absence of 5 days of on-therapy data. A total of 6.3% of subjects used concomitant VMS therapy and were not excluded from the study. Due to the small number of subjects, the impact of this protocol violation on the study results is suspected to be small.

Concomitant Medications:
Concomitant therapy occurred in 287 (90%) of subjects during the on-therapy phase and was balanced between the BZA/CE groups (91%). The placebo rate was slightly lower at 86%. The most common medications were anti-inflammatory/anti-rheumatics and other analgesics/antipyretics. The sponsor reports that 6.3% of subjects were taking concomitant therapy to treat VMS symptoms. As a result the Per Protocol analysis, which excluded subjects with unacceptable concomitant medication and selected other protocol violations, was queried.

Phase 3 Trial 306

(b) (4)

[redacted]

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(b) (4)

[redacted]

[redacted]

Phase 3 Trial 3307

Study 3115A1-3307-WW (referred to hereafter as 3307) and entitled "A double blind, randomized, placebo- and active-controlled efficacy and safety study of the effects of bazedoxifene/conjugated estrogen combinations on endometrial hyperplasia and prevention of osteoporosis in postmenopausal women" was a 1-year, multicenter, double-blind, randomized, placebo and active controlled study. The study randomized 1886 healthy postmenopausal women (40 to <65 years of age) with an intact uterus into five dose groups: BZA 20/CE 0.625 mg, BZA 20/CE 0.45 mg, BZA 20 mg, CE 0.45/MPA 1.5 mg, or placebo. The study was to assess endometrial safety at 1 year, and BMD at 1 year in the Osteoporosis Substudy (OSS). A total of 590 subjects were randomized into the Osteoporosis Substudy and subjects had to be within 5 years of menopause with at least 12 months of spontaneous amenorrhea or 6 months with elevated FSH. The exclusion criteria were similar to study 303. Breast density, uterine spotting/bleeding, bone turnover markers and sleep parameters were also assessed.

Efficacy endpoints - Trial 3307:

Primary:

- Incidence of endometrial hyperplasia (Efficacy Evaluable Population: defined as subjects who were randomly assigned and took at least 1 dose of the test article, who had a screening endometrial biopsy with readings by at least 2 blinded central pathologists, had a biopsy during Month 12, or had hyperplasia diagnosed before Month 12 and had no major protocol violations.
    - Subjects were excluded from the EE analysis population if they had a reading of hyperplasia by any pathologist at baseline, or had biopsies taken after another prohibited hormone medication had been administered. Subjects who had endometrial malignancy were not included in the numerator or denominator of the incidence calculation for the EE population.
- Bone Mineral Density at the Lumbar Spine at Month 12 (Osteoporosis Substudy)

Secondary:

- Bone Mineral Density (OSS)
    - Lumbar spine at Month 6
    - Total Hip at Month 12
    - Femoral Neck at Month 12

- Bone Turnover Markers (OSS)
- Sleep (Medical Outcomes Study Sleep Scale)
- Menopause Quality of Life Questionnaire (MENQOL)
- Breast Density
- Breast Tenderness
- Amenorrhea

Safety endpoints - Trial 3307:
Safety variables included scheduled physical examinations (including breast examinations), pelvic examinations, vital signs (including blood pressure (BP) and weight), endometrial biopsies, pap smears, clinical laboratory evaluations, TVUs, ECGs, and mammograms.

Adverse events: Special adverse events, including but not limited to ischemic cardiac events, cerebrovascular events and thromboembolic events, were identified using standardized MedDRA queries (SMQ) of ischemic heart disease, central nervous system hemorrhage, cerebrovascular accidents, and embolic and thrombotic events.

Statistical Considerations - Trial 3307:
The efficacy endpoints, which included BMD and BTMs, were analyzed according to the treatment group that the subjects were randomly assigned. The safety endpoints were analyzed according to the treatment that the subjects actually received. Where multiple p-values are presented, these are not controlled for multiplicity unless otherwise specified.

Sample size for the BZA/CE treatment groups was based on the endometrial hyperplasia endpoint. Based on FDA guidance document stating endometrial hyperplasia observed rate at year 1 had to be less than or equal to 1% with the upper limit of the 1-sided 95% confidence interval (CI) less than 4%, a sample size of 300 subjects having at least 1 year follow-up in each BZA/CE treatment group was sufficient. This would provide more than 80% statistical power, on the assumption that the population rate for the incidence of endometrial hyperplasia is 0.26%. A total enrollment of 430 in each BZA/CE group would ensure 300 completers. A total of 215 would be enrolled in the BZA and CE/MPA groups.

The sample size for the OSS was based on the differences between BZA/CE and placebo treatment groups in the mean percentage changes in lumbar spine and hip BMD at 1 year. For lumbar spine, the true difference was assumed to be 2.5% with a standard deviation (SD) of 3.5%. For total hip, the true difference was assumed to be 1.5% with a SD of 3.0%. The sample size required for 90% power based on the total hip BMD was 84 per treatment group, and was 42 per treatment group for the lumbar spine comparison. A total of 150 subjects in the placebo and each of the BZA/CE treatment groups and 75 subjects in the BZA and CE/MPA treatment groups, respectively, would be enrolled. If 85% of these subjects had at least 1 post-baseline BMD assessment for

this analysis, then each comparison of treatment with placebo would have at least 90% power.

For the breast density substudy, the non-inferiority margin was set as 1.5%. The objective was to demonstrate that treatment with BZA/CE was not worse than placebo by more than 1.5% at 1 year. Therefore, the null hypothesis of inferiority was that the population mean breast density difference, placebo minus BZA/CE, was less than or equal to -1.5% (that is, BZA/CE was worse than placebo by at least 1.5%). With an assumed SD of 4%, 150 subjects per treatment group were required for 90% power to reject this null hypothesis using a 1-tailed p=0.025 comparison, when the population mean difference was 0. Equivalently, the probability that the lower limit of the 95% CI on the mean difference, placebo minus BZA/CE, was greater than -1.5 % was at least 90% if the populations mean difference was 0 and the sample size per treatment group was at least 150.

Reviewer's comment: The rationale for the chosen non-inferiority margin in the breast study was not provided in the study report.

The effect of BZA/CE on VMS and sleep parameters at Months 3 and 12 were assessed in the subjects who met the criteria for the sleep substudy. Assuming that 25% of subjects met the inclusion criteria and were included in the analysis, the estimated sample size (approximately 75 subjects in the BZA/CE treatment groups and placebo) provided 85% power to detect a difference of 1 point versus placebo (SD approximately 2.0) on the VMS subscore of MENQOL and an effect size of 0.5 on the sleep disturbance subscore of MOS Sleep Scale, separately.

Reviewer's comment: The sleep and breast density questionnaires and associated measurements associated are considered exploratory secondary endpoints and will not support labeling. These tools were not submitted to SEALD for evaluation.

Disposition– Trial 3307:

A total of 4774 were screened with 1886 subjects enrolled/randomized into the 5 treatment groups in a 2:2:1:1:2 ratio. A total of 1843 subjects took at least one dose of the test article and were included in the safety analysis. Enrollment across the substudies is shown in Table 18.

Table 18: Safety Population (dosed subjects) across Substudies

	CE 0.45/BZA 20	(b) (4)	BZA 20	CE 0.45/MPA 1.5	Placebo	Total
Main Study	445		230	220	474	1843
OSS	135		73	70	158	590
Sleep Study	115		49	56	116	459
Breast Study	231		122	100	240	940

Overall, 1477 (80.1%) of subjects completed the study. See Table 19. Overall in the main study, there was an imbalance in discontinuations in CE/MPA arm at 27.7% compared to 17-20% in the remaining groups, including placebo. The greatest reason for discontinuation in the study was adverse events (8% overall and 14% in the CE/MPA arm). Discontinuation due to subject request was the second highest reason at 3.8% overall and 6.1% in CE 0.45/BZA 20 group.

Table 19: Number of subjects who completed and discontinued study by primary reason

Conclusion Status Reason[a]	Overall p- Value[b]	BZA 20 mg /CE 045 mg	BZA 20 mg /CE 0.625 mg	BZA 20 mg	CE 0.45 mg /MPA 1.5 mg	Placebo	Total
Total		445 (100)	(b) (4)	230 (100)	220 (100)	474 (100)	1843 (100)
Completed	0.027	357 (80.2)		185 (80.4)	159 (72.3)	383 (80.8)	1477 (80.1)
Discontinued	0.027	88 (19.8)		45 (19.6)	61 (27.7)	91 (19.2)	366 (19.9)
Adverse event	0.012	34 (7.6)		16 (7.0)	31 (14.1)	33 (7.0)	147 (8.0)
Death	0.576	0		0	0	1 (0.2)	1 (0.1)
Investigator request	0.576	0		0	0	0	1 (0.1)
Lost to follow-up	0.092	8 (1.8)		11 (4.8)	8 (3.6)	9 (1.9)	46 (2.5)
Other	0.043	6 (1.3)		6 (2.6)	2 (0.9)	15 (3.2)	33 (1.8)
Protocol violation	0.110	8 (1.8)		4 (1.7)	9 (4.1)	5 (1.1)	35 (1.9)
Subject request	0.016	27 (6.1)		2 (0.9)	7 (3.2)	16 (3.4)	70 (3.8)
Unsatisfactory response (efficacy)[c]	0.376	5 (1.1)		6 (2.6)	4 (1.8)	12 (2.5)	33 (1.8)

a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject;
b. P-value for 5x2 contingency table based on Chi-square test.
c. Reasons were unspecified.

Source: Table 8-2, p. 63 CSR 3307

In the Osteoporosis Substudy, an imbalance in discontinuation was seen in the CE/MPA group (27.1%) and BZA 20 mg group (24.7%) compared to 15-18% in the remaining groups. Adverse events (7.3% overall) and subject request (4.1% overall) were the top reasons. In the breast study, imbalances were again seen in the CE/MPA dose group with an overall discontinuation rate of 24% (vs 18.1% overall) and discontinuation due to adverse events rate of 13% (vs 7.2% overall). The sleep study showed an even higher discontinuation rate in the CE/MPA of 33.9% vs 20.5% overall, with discontinuation due to adverse event rate of 17.9% vs 8.3% overall.

Reviewer's comment: Due to the small imbalances (up to 3%) in discontinuation rate and adverse events, it is unlikely the imbalances affected efficacy results.

Unblinding: Four subjects had their blind broken due to safety. There were three events of breast cancer (CE/MPA, CE 0.45/BZA 20, and placebo), and one event of migraine with aura (CE 0.625/BZA 20). Three additional subjects unblinded themselves (b) (4) (2 in the CE 0.45/MPA, and 1 in BZA 20mg) and were withdrawn due to protocol violation.

Protocol Violations – Trial 3307

A total of 412 (22.4%) subjects had protocol deviations and the deviations were generally evenly distributed across treatment groups. A total of 143 (7.8%) subjects were randomized without having met inclusion and/or exclusion criteria. Selected violations include: not postmenopausal (0.6%), PMP >5 years (0.7%), prohibited use of hormones prior to screening (0.7%), and taking bone active drugs prior to screening (2.5%) A total of 210 (11.4%) subjects had protocol deviations that occurred while on-therapy. Selected violations include: endometrial biopsy not repeated when >4 mm or insufficient tissue (0.5%), prohibited use of bone active drugs (3.9%), and incorrect dose of study drug in breast density substudy (6.1%). The sponsor states these deviations did not alter the results for endometrial safety or BMD LS or total hip.

Reviewer's comment: For the bone active drug there was some variation across doses ranging from 2.6% (BZA 20/CE 0.45) to 4.4% (placebo and CE 0.625/BZA 20). In the breast density study, the violations ranged from 4.3% to 7% across treatment groups. It is unclear if these violations alter results. For the OSS, the sponsor was asked to provide a listing of the drug name, duration of bone active therapy and BMD effect for individual subjects. See results section for further discussion.

A total of 35 (1.9%) subjects were withdrawn from the study because of protocol violations. Before unblinding, the sponsor identified those subjects who were to be excluded from the efficacy analysis based on inclusion and exclusion criteria, use of prohibited treatments, and compliance with taking the test article. Eight subjects (<1%) were excluded from endometrial hyperplasia EE population. Four subjects (<1%) were excluded from the LS BMD MITT population, and 171 (18%) were excluded from the breast density study due to absence of baseline breast density data.

Reviewer's comments: 1) Overall, the rate of violations in the breast study due to absence of baseline breast density data appears high. Subjects who were not participating in the breast density substudy only had to have a mammogram within 3 months of randomization, while subjects entering the breast substudy had to have a digital mammogram at baseline. It is conceivable that this entry criterion may have been overlooked at entry or potentially enrollment could have been retroactive.
2) The rate of excluded subjects from breast density study in CE 0.45/MPA group appears unbalanced at 26% (26 out of 100 total subjects) Table 20. This imbalance in the comparator arm should not affect the overall study results.

Table 20: Breast Density - MITT/PP Population Exclusions

Reason for Protocol Violation	CE 0.45 /BZA 20	CE 0.625 /BZA 20	BZA 20	CE 0.45 /MPA 1.5	Placebo	Total
MITT Population						
Did not have at least 1 baseline breast density datapoint	41 (18)	(b) (4)	21 (17)	26 (26)	41 (17)	**171 (18)**
PP Population						
Did not have at least 1 baseline breast density datapoint	41 (18)		21 (17)	26 (26)	41 (17)	**171 (18)**
<80% medication	0		1 (<1)	0	3 (1)	**5 (<1)**
Source: Excepted from Table 8-7, p. 76, 3307 CSR						

Concomitant Therapy:
Approximately 99.6% of subjects used non-study medication and the class/category of medication used was balanced between treatment groups. Calcium was the most frequently used medication and was used by 98.5% of subjects in the main study and 99% in the OSS. Other frequently used medication classes were vitamins A and D and combinations (97.2%), anti-inflammatory/antirheumatic products, nonsteroidals (54.4%); other analgesics and antipyretics (51.9%); multivitamins combination (32.6%); and cholesterol; triglyceride reducers (25.8%) and antihistamines (25.4%). No imbalance was observed among treatment groups.

Reviewer's comment: Per sponsor report, the incidence of subjects on bone active drug ranged from 2.6% (BZA 20/CE 0.45) to 4.4% (placebo and CE 0.625/BZA 20) On April 9, 2013, the sponsor submitted datasets and analyses of subjects taking bone active medications. The lumbar spine summary table reports 21 such subjects across dose groups – Three subjects each in the CE 0.625/BZA 20 and CE/MPA groups, 6 subjects in the CE 0.45/BZA 20 group, 2 subjects in the BZA 20 group, and 7 subjects in placebo. The accompanying dataset contains 23 subjects (an additional one subject was found in the BZA 20/CE 0.625 and BZA 20 groups. All reported medications (i.e., NSAIDs, Synthroid, etc.) had the potential to decrease BMD.

Ancillary Breast Prevention/Mammogram Substudy -Study 4000

Study 4000 was an ancillary, post-hoc, non-interventional study of Study 303. The only objective was to evaluate quantitative changes in mammographic breast density at baseline and after 24 months of therapy in postmenopausal women who had received daily treatment with either BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, raloxifene 60 mg, or placebo and had baseline and Month 24 mammograms. Overall, BZA/CE did not affect the age-related changes in mammographic breast density over 24 months.

Reviewer's comment: This post-hoc study will not support labeling for breast prevention.

6 Review of Efficacy

6.1 Treatment of Moderate to Severe Vasomotor Symptoms

6.1.1 Methods

The clinical program for the treatment of moderate to severe vasomotor symptoms included one pivotal study, Trial 305 – a 12-week, double-blind, randomized, placebo and active controlled study and one supportive study, Study 303 –a 24-month study that collected hot flush data at Week 4 and Week 12. Study 305 enrolled subjects with at least 7 moderate or severe hot flushes per day or at least 50 per week during the screening week. Enrollment in Study 303 was not based on any hot flush frequency or severity requirement. For the Study 303 VMS assessment, the sponsor prospectively included subjects from the total population who had at least 7 moderate or severe hot flushes per day or at least 50 per week during the screening week, however, the number of subjects was not pre-defined. In addition, the number of hot flushes at baseline were unbalanced between treatment groups. Due to the enrollment process, sample size, and multiplicity adjustments, Study 303 was deemed supportive and will be discussed separately.

For Study 305, the Per Protocol population was included in order to compare effects when subjects without the prerequisite number of baseline hot flushes (at least 7 moderate or severe hot flushes per day or at least 50 per week during the screening week) were excluded, n=17 (5%). See Section 5.3 for full definition of the Per Protocol population.

6.1.2 Demographics

Study 305
There were no significant demographic differences among the treatment groups (Table 21). Most subjects were White, had an intact uterus, and had undergone natural menopause. Subjects were healthy postmenopausal women, with a mean age of 53.4 years (age range between 42 and 64 years) with a mean body mass index of 26.2 kg/m^2. The mean years since menopause was 4-5 years.

Table 21: Demographic and Baseline Characteristics, Safety population- Study 305

Characteristic	p-Value	BZA 20 mg/ CE 0.45 mg (n = 127)	BZA 20 mg/ CE 0.625 mg (b) (4)	Placebo (n = 63)
Age (years)				
Mean	0.666[a]	53.57		53.62
Standard deviation		4.82		5.31
Minimum - maximum		42.00 -64.00		45.00 - 63.00
Ethnic origin	0.368[b]			
Hispanic or Latino		10 (7.87)		3 (4.76)
Non-Hispanic and Non-Latino		117 (92.13)		60 (95.24)
Race	0.813[b]			
Black or African American		11 (8.66)		7 (11.11)
Other		4 (3.15)		3 (4.76)
White		112 (88.19)		53 (84.13)
BMI (kg/m^2)				
Mean	0.804[a]	26.37		26.03
Standard deviation		3.91		4.19
Minimum - maximum		17.40 - 35.50		17.10 - 34.00
Years since last menstrual period				
Mean	0.558[a]	4.69		4.84
Standard deviation		4.18		4.59
Minimum - maximum		0.58 - 21.78		0.52 - 19.44
Type of menopause	0.475[b]			
Natural		127 (100)		63 (100)
Surgical (bilateral oophorectomy)		0		0

Source: Table 8-6, p. 40 CSR

Trial 303

The VMS population, referred to as EE1 by the sponsor, represented a smaller subpopulation of the main 303 study. The baseline characteristics of the VMS subpopulation (n=217) were similar than the larger study population (n=3544) but differed somewhat in that patients in the VMS subpopulation were slightly younger (mean age 54.7 vs 56.5 years) and had more recent onset of menopause (mean 6.2 yrs vs 8.1 years).

Table 22: Trial 303 - VMS Subpopulation EE1

Characteristic	CE 0.45/ BZA 10	CE 0.45/ BZA 20	CE 0.45/ BZA 40	CE 0.625/ BZA 10	CE 0.625/ BZA 20	CE 0.625/ BZA 40 (b) (4)	placebo	raloxifene
	N=29	N=28	N=24				N=33	N=24
Age (yrs)	53.8	54.6	54.3				54	55.6
Ethnic Origin								
Hispanic	1	1	1				2	2
Non-Hispanic	28	27	23				31	22
Race								
Black	4	4	3				1	1
Other	1	1	1				2	2
White	23	23	20				29 (54%)	21 (88%)
BMI (kg/m2)	26.3	25.7	25.6				24.7	25.7
Yrs since menopause	6.0	6.7	5.6				6.8	6.6
Source: Compiled by reviewer, ISE dataset ptinfo.xpt								

Subjects in Study 305 and the VMS subpopulation of Study 303 were similar with the exception that the mean years since menopause was even lower in Study 305 at 4.3-4.8 years.

6.1.3 Subject Disposition

Trial 305

A total of 1093 subjects were screened for enrollment with 332 subjects randomized. The most common reasons for screen failure were ineligible transvaginal ultrasound, risk of noncompliance, ineligible screening endometrial biopsy, not seeking treatment for HF or did not meet entry criteria for frequency of HF, ineligible breast exam or mammogram results, and ineligible AST or ALT at screening.

Of the 332 randomized, 14 did not use the test article. The remaining 318, who completed the pre-study period and took at least 1 dose of test article, were included in the safety population. Eight subjects were excluded from the MITT population because they did not have 5 days of on-therapy data leaving a total of 310 subjects in the MITT population. Overall, 277 (87%) subjects completed the study. The breakdown per treatment group is shown in Table 23.

Table 23: Subject Status: Number (%) of subjects by Population Subset

Population Subset	BZA 20 mg/ CE 0.45 mg	BZA 20 mg/ CE 0.625 mg	Placebo	Total
Randomly assigned	133	(b) (4)	66	332
Test article not used	6		3	14
Safety population[a]	127 (100)		63 (100)	318 (100)
Excluded from MITT for VMS[b]	5 (4)		0 (0)	8 (3)
MITT population for VMS[b]	122 (96)		63 (100)	310 (97)
Completed study	113 (89)		53 (84)	277 (87)

a. Safety population included all randomly assigned subjects who took at least 1 dose of test article.
b. MITT population included subjects who were randomly assigned to test article, took at least 1 dose of test article, had at least 5 days of data at baseline, and had at least 5 days of VMS data during the on-therapy period.

Abbreviation: BZA = bazedoxifene; CE = conjugated estrogens; MITT = intent to treat; VMS = vasomotor symptoms.

Source: Hand tabulated by writer from these CDRs: CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1 BAZEDOXIFENE-CE/305/305_NDA_CDRs_2007/305_DOSED_QUALSITES/3115-305 demo5.lst 23MAR07 10:47, MITT4_SYM 21MAR07 14:24; and / 305_NODOSE_QUALSITES/3115-305 demo5.lst, 23MAR07 10:56.

Source: Table 8-1, p.34, Study 305 CSR

Overall, a total of 12.9% of subjects withdrew from the study including 12.0% from the BZA/CE groups combined and 16% from the placebo group. See Table 24. Adverse events and protocol violations were the most frequent reasons for discontinuation. (b) (4) When the lost-to-follow group was queried, only 2 of the 5 subjects could be reliably located (dataset conclus.xpt). Subject 305-521-501056 moved out of state and subject 305-530-500910 did not show for the visit. Both subjects were

taking BZA20/CE 0.625. A third subject (305-521-501056) had elevated AST/ALT and the declined repeat labs and was in the placebo group. It does not appear that adverse events in this group led to the imbalance.

Table 24: Study 305 - Number (%) of Subject Who Withdrew from Study

Conclusion Status Reason	Overall p-Value	BZA 20 mg/ CE 0.45 mg n = 127	BZA 20 mg/ CE 0.625 mg (b) (4)	Placebo n = 63
Discontinued	0.634	14 (11.0)		10 (15.9)
Adverse event	0.071	5 (3.9)		6 (9.5)
Lost to follow-up	0.023*	0		0
Protocol violation	0.727	5 (3.9)		2 (3.2)
Subject request	0.598	3 (2.4)		1 (1.6)
Unsatisfactory response - efficacy	0.840	1 (0.8)		1 (1.6)

a. Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
b. Chi-square.
Statistical significance at the 0.05, 0.01, 0.001 levels is denoted by *, **, *** respectively.

Source: Table 8-2, p. 36

Study 303

For the VMS assessment, the sponsor prospectively included only subjects with at least 7 moderate or severe hot flushes per day or at least 50 per week during the screening week (subpopulation EE1), however, the number of subjects was not pre-defined and a number of subjects enrolled in each group was small, n=217 subjects (13-33 subjects per group. A high number of subjects (31%) in the VMS subpopulation discontinued the study. (b) (4) 14% in the CE 0.45/BZA 20 group due to adverse events and subject request. The placebo group had discontinuation rate of 57% which was driven by unsatisfactory response and adverse events.

Table 25: Study 303 - Discontinuations -Vasomotor Subpopulation – EE1

	CE 0.45/BZA 10	CE 0.45/BZA 20	CE 0.45/BZA 40	CE 0.625/BZA 10	CE 0.625/BZA 20	CE 0.625/BZA 40	PBO	RAL	Total
Total N	N=29	N=28	N=24	(b) (4)			N=33	N=24	N=217
Discontinued	8 (28%)	4 (14%)	9 (38%)				19 (57%)	6 (25%)	69 (31%)
Death	0	0	0				0	0	
AE	3	1	3				7	4	
Failed to Return	2	1	1				1	0	
Other	1	0	2				0	1	
Protocol Violation	1	0	0				1	0	
Subject request	1	1	1				2	0	
Unsatisfactory response	0	1	2				8	1	

Source: Reviewer compiled from conclus.xpt, ISE

6.1.4 Analysis of Primary Endpoint(s)

Study 305 (Pivotal Study)

Baseline values
Baseline values for the average number of daily hot flushes (10.3-10.5 HF per day) and average daily severity score (2.3) for the CE 0.45/BZA 20 and CE 0.625/BZA 20 groups (MITT) are shown in Table 26.

Table 26: Study 305 - Baseline Mean (SD) Values for Primary and Secondary Endpoints (MITT)

Endpoints	BZA 20 mg/ CE 0.45 mg	BZA 20 mg/ CE 0.625 mg	Placebo
Primary efficacy endpoints			
Average daily number of moderate and severe hot flushes	10.3 (5.38)	(b) (4)	10.5 (4.96)
Average daily severity score of hot flushes	2.3 (0.31)		2.3 (0.33)
Other endpoints of interest			
Average daily number of mild, moderate, and severe hot flushes	11.7 (5.77)		12.1 (5.57)
Daily composite score	27.2 (15.92)		27.6 (14.23)
MOS sleep scale (sleep index I)[a]	43.3 (18.1)		40.1 (17.2)
MENQOL (total score)	4.46 (1.24)		4.50 (1.109)

Baseline values were determined from the 7 consecutive days of data collected before subjects were randomly assigned to test article.

Source: Table 9-1, p. 42

Reviewer's comment: Given the low number of affected subjects and the differences between groups were highly significant, the original analysis (original MITT population) will be presented.

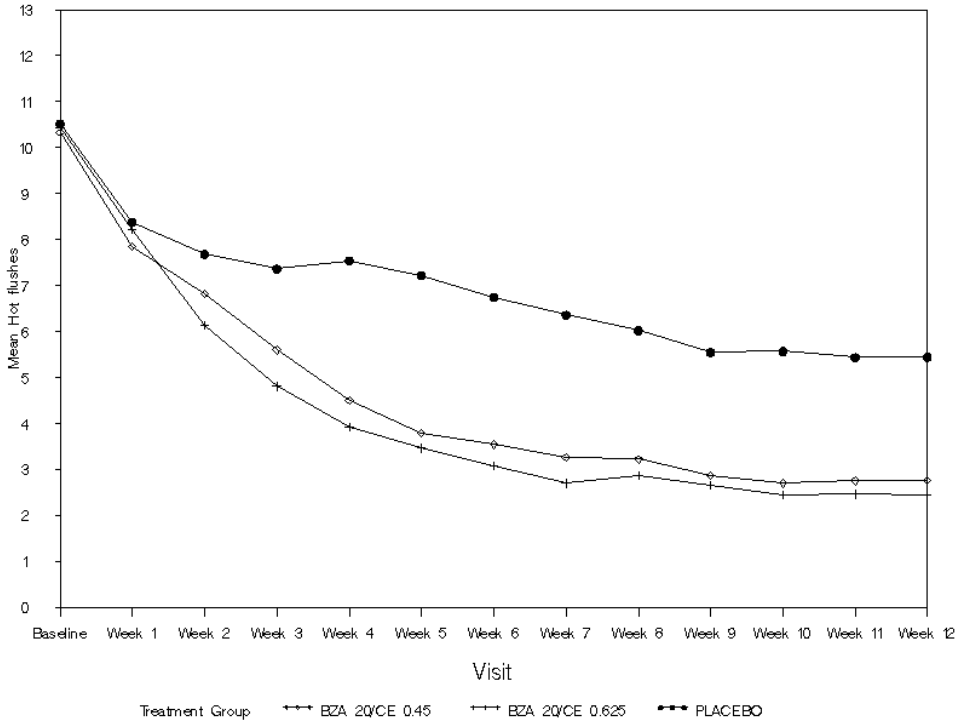
Reduction in the Frequency of Hot Flushes
The change from baseline in the average daily number of moderate and severe hot flushes is shown in Table 27. There was a significant decrease ($p<0.001$) in the mean number of moderate and severe HF (range, -6 to -8) at Weeks 4 and 12 in both BZA/CE groups, the placebo subtracted values for BZA 20/CE 0.625 and BZA 20/CE 0.45 were -(b) (4) and -3.07 at Week 4, and (b) (4) and -2.71 at Week 12, respectively. There was a (b) (4) and 80% reduction from baseline in the BZA 20/CE 0.625 and BZA 20/CE 0.45, respectively, compared to 51% in the placebo group. The MITT and PP analyses were similar. The effect on hot flushes across Weeks 1 through 12 is shown in Figure 3 (MITT) (b) (4) The placebo-subtracted effect at Week 12 was less than at Week 4 due to the placebo effect over time.

Table 27: Adjusted Mean Change from Baseline in the Average Daily Number of Hot Flushes (Original MITT)

	BZA 20 mg/ CE 0.45 mg	BZA 20 mg/ CE 0.625 mg	Placebo
Week 4			
N	**122**	(b) (4)	**63**
Mean Change	**-5.90**		**-2.84**
Difference from Placebo (95% C.I.)	**-3.07 (-4.40, -1.73)***		
Week 12			
N	**122**		**63**
Mean Change	**-7.63**		**-4.92**
Difference from Placebo (95% C.I.)	**-2.71 (-3.84, -1.57)***		

Statistical Reviewer's Analysis
*p<0.001
[1] Based on raw data analysis using ANCOVA model: Difference= Treatment + Baseline + Site

Figure 3: Study 305 - Average Daily Number of Moderate and Severe HF, Week 1 through Week 12 (MITT, LOCF) (Fig. 9-1, p. 45, 305 CSR)



Reviewer's comment: Both BZA 20/CE 0.625 and BZA 20/CE 0.45 doses show efficacy in reducing the frequency of hot flushes at 4 and 12 weeks with placebo-subtracted changes greater than 2 hot flushes/day using either MITT or PP.

Reduction in the Severity of Hot Flushes

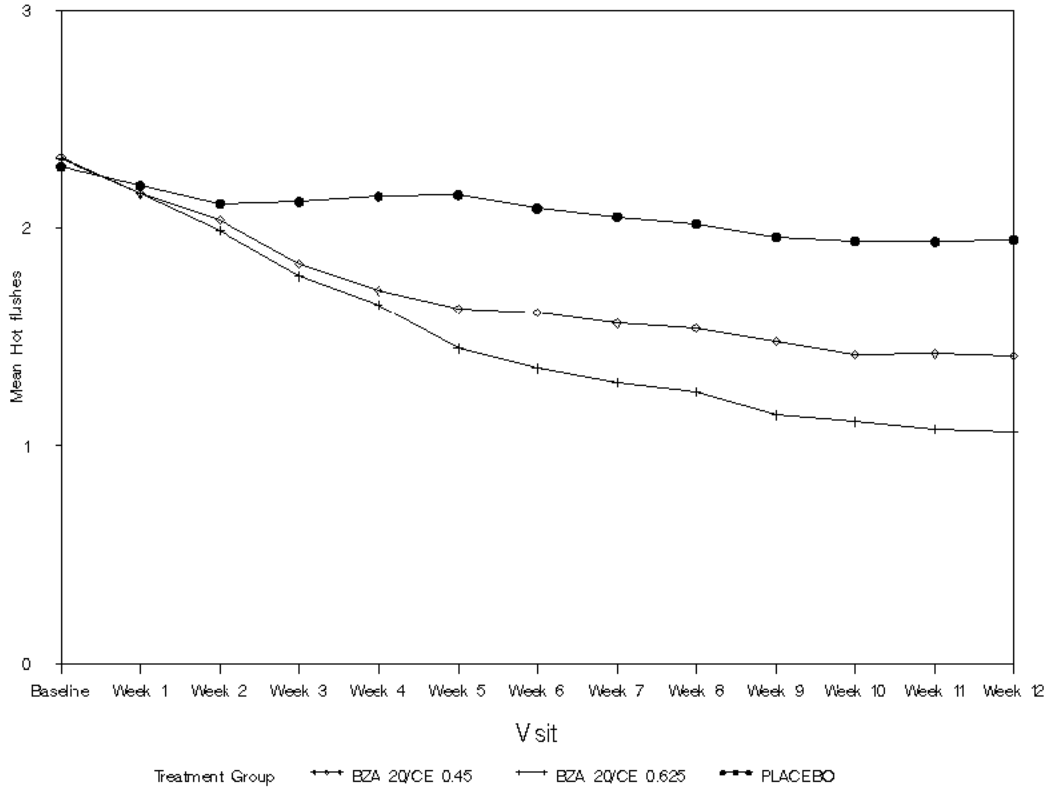
The change from baseline in average daily severity score of hot flushes is shown in Table 28. There was a significant reduction ($p<0.001$) in the severity score of hot flushes (range, -0.6 to -1.2) at Weeks 4 and 12 in both BZA/CE groups with placebo-subtracted values between -0.49 to -0.95 (Original MITT). The MITT and PP analyses were similar. Figure 4 shows the reduction across all weeks (MITT). (b) (4)

Table 28: Adjusted Mean Chang from Baseline in Average Daily Severity of Hot Flushes (Study 1)

	BZA 20 mg/ CE 0.45 mg	BZA 20 mg/ CE 0.625 mg	Placebo
Week 4		(b) (4)	
N	**122**		**63**
Mean Change[1]	**-0.58**		**-0.09**
Difference from Placebo (95% C.I.)[2]	**-0.48 (-0.70, -0.27)***		
Week 12			
N	**122**		**63**
Mean Change[1]	**-0.87**		**-0.26**
Difference from Placebo (95% C.I.)[2]	**-0.60 (-0.86, -0.35)***		

Statistical Reviewer Analysis
*p<0.001
[1] Change from baseline using raw data
[2] Based on raw data analysis using ANCOVA model: Difference= Treatment + Baseline + Site

Figure 4: Study 305 - Average Daily Severity Score of HFs, Weeks 1 Through 12, MITT (LOCF)



Source: Fig. 9-2, p.47

Reviewer's comment: Both CE 0.625/BZA 20 and CE 0.45/BZA 20 doses showed efficacy in decreasing the severity of HFs at Weeks 4 and 12 with placebo-subtracted values between -0.49 to -0.95. (b) (4)

Study 303 (Supportive Study)

Baseline values

Baseline values for the number and severity of moderate and severe hot flushes are shown in Table 29, Column 1. There was an imbalance in the number of hot flushes at baseline across groups with (b) (4) and 11.4 hot flushes for CE 0.625/BZA 20 and CE 0.45/BZA 20 dose groups, respectively, compared to 14.3 hot flushes for placebo. The baseline hot flush severity of moderate and severe hot flushes was similar between groups with severity scores of (b) (4) and 2.56, for CE 0.625/BZA 20 and CE 0.45/BZA 20 dose groups, respectively, compared to 2.52 for placebo (Column 3).

Reviewer's comment: Based on prior communication with the sponsor (meeting minutes/special protocol assessments), the baseline severity score was to be based on the pre-specified method using only moderate and severe hot flushes (shown in Column 3, Table 25). Column 2 represents baseline severity scores including mild hot flushes. When comparing Column 2 and Column 3, the addition of mild hot flushes dilutes the baseline score, making any treatment effect smaller but this difference does not appear to be clinically meaningful. The addition of mild hot flushes may also confound the efficacy results as mild hot flushes tend to resolve without treatment. Efficacy results using Column 3 as baseline, the pre-specified approach, were submitted by the sponsor (as an alternative approach). After discussion with the statistical reviewer, the severity analysis will rely upon baseline data from Column 2 since 1) subjects evaluated in the analysis had moderate or severe HFs at baseline, 2) there is an absence of clinically meaningful changes between calculations, and 3) the current Division standard is to include mild/moderate/and severe HFs at baseline.

Table 29: Study 303 -Baseline Hot Flushes -Number and Severity (EE1, LOCF)

		Column 1		Column 2		Column 3	
		Number Mod and Severe HF		Severity HF (based on mild/mod/severe)		Severity HF (based on mod/severe)	
	N	**Mean**	SD	**Mean**	SD	**Mean**	SD
CE 0.625 with							
10 mg BZA	[redacted] (b) (4)						
20 mg BZA							
40 mg BZA							
CE 0.45 with							
10 mg BZA	29	**10.48**	4.32	**2.35**	0.40	**2.42**	0.36
20 mg BZA	28	**11.44**	4.92	**2.45**	0.35	**2.56**	0.32
40 mg BZA	24	**10.70**	3.74	**2.41**	0.43	**2.50**	0.39
Raloxifene	24	**12.00**	4.67	**2.37**	0.44	**2.54**	0.33
Placebo	33	**14.32**	12.94	**2.39**	0.42	**2.52**	0.36

Source: Table 9-22, p. 131 and Table 15.66, p. 950, 303 CSR

Reduction in the Frequency of Hot Flushes

Results in the mean change in the number of hot flushes from baseline at Week 4 and Week 12 are shown in Table 30. In order to address multiplicity, the step-down procedure included the following hierarchy: BZA 10/0.625 first, BZA 20/0.625, BZA 40/0.625, then the 0.45 dose regimens. In addition, each dose had to show statistical significance at both the Week 4 and Week 12 before proceeding to the next group. Based on these guidelines, [redacted] (b) (4) The mean change from baseline for CE 0.625/BZA 20 was [redacted] (b) (4) (Week 4) and [redacted] (b) (4) (Week 12) with placebo-subtracted values of [redacted] (b) (4) respectively. These results meet the criteria for efficacy based on the

draft guidance (difference of >2 hot flushes/day). No significant changes were seen when data from subjects with missing source documentation were excluded.

Table 30: Study 303 - Mean Change from Baseline in Number of Hot Flushes at 4 and 12 Weeks, Efficacy Evaluable 1 population, LOCF

		Original Analysis (sponsor)					Excluding Missing Source Documentation (sponsor)				
	Week	N	Adjusted mean change Mean	SE	p-value vs placebo	Placebo subtracted value[#]	N	Adjusted mean change Mean	SE	p-value vs placebo	Placebo subtracted value
CE 0.625 with											
10 mg BZA	4	[redacted]									
	12										
20 mg BZA	4										
	12										
40 mg BZA	4										
	12										
CE 0.45 with											
10 mg BZA	4	29	-7.53	1.04	<0.001	-5.62	26	-7.53	1.11	<0.001	-5.79
	12	29	-8.98	1.08	<0.001	-6.53	26	-9.36	1.16	<0.001	-7.03
20 mg BZA	4	28	-5.23	1.05	0.022	-3.32	25	-5.70	1.13	0.009	-3.96
	12	28	-8.74	1.14	<0.001	-6.29	25	-8.71	1.18	<0.001	-6.38
40 mg BZA	4	24	-5.12	1.14	0.034	-3.21	23	-5.28	1.18	0.023	-3.74
	12	24	-5.53	1.18	0.049	-3.08	23	-5.55	1.24	0.047	-3.22
Raloxifene	4	24	-4.74	1.13	--	-2.83	NR	NR	NR	NR	--
	12	24	-5.29	1.18	--	-2.84	NR	NR	NR	NR	--
Placebo	4	33	-1.91	0.98	--	--	32	-1.74	1.01	--	--
	12	33	-2.45	1.02	--	--	32	-2.33	1.06	--	--

[#]Calculated by reviewer NR=not reported
Source: Table 9-23, p. 132, 303 CSR

Reduction in the Severity of Hot Flushes
The mean change from baseline in the severity of HFs from baseline at Week 4 and Week 12 is shown in Table 31. [redacted]

Similar results were seen using the alternative analysis (not shown).

Table 31: Study 303 - Mean Change from Baseline in Severity of HFs at 4 and 12 Weeks, Efficacy Evaluable 1 population, LOCF

		Original Analysis (sponsor)*					Excluding Missing Source Documentation (sponsor)				
	Week	N	Adjusted mean change Mean	SE	p-value vs placebo	Placebo subtracted value[#]	N	Adjusted mean change Mean	SE	p-value vs placebo	Placebo subtracted value
CE 0.625 with											
10 mg BZA	4	(b) (4)									
	12										
20 mg BZA	4										
	12										
40 mg BZA	4										
	12										
CE 0.45 with											
10 mg BZA	4	29	-0.85	0.13	<0.001	-0.62	26	-0.95	0.14	0.002	-0.58
	12	29	-1.22	0.15	<0.001	-1.01	26	-1.37	0.16	<0.001	-1.03
20 mg BZA	4	28	-0.38	0.13	0.406	-0.15	25	-0.50	0.14	0.508	-0.13
	12	28	-1.00	0.15	<0.001	0.79	25	-1.03	0.16	0.001	-0.69
40 mg BZA	4	24	-0.45	0.14	0.256	-0.22	23	-0.59	0.15	0.276	-0.22
	12	24	-0.46	0.17	0.246	-0.25	23	-0.61	0.17	0.227	-0.27
Raloxifene	4	24	-0.20	0.14	--	--	NR	NR	NR	NR	--
	12	24	-0.22	0.17	--	--	NR	NR	NR	NR	--
Placebo	4	33	-0.23	0.12	--	--	32	-0.37	0.13	--	--
	12	33	-0.21	0.14	--	--	32	-0.34	0.14	--	--

[#]Calculated by reviewer
*Baseline severity score = mild, moderate and severe hot flushes
Source: Table 9-24, p. 133, 303 CSR and Efficacy Amendment, Question 2, 2-19-13,p.15

Reviewer's comment: Due to the design of Study 303 and limited enrollment, (b) (4) CE 0.45/BZA 20 doses showed efficacy in reducing the number or severity of hot flushes.

6.1.7 Subpopulations

In Study 305, the analysis of the number of hot flushes and the severity of hot flushes was performed for the first 12 weeks on therapy for the following age subgroups: < 50, 50 to 59, and > 59 years of age. The mean changes were similar across age groups although the sample sizes in the <50 and >59 groups were small and statistical significance varied (Table 32). No efficacy differences are suggested based on age.

Table 32: Study 305 -Mean (SE) Change from Baseline by Age Group in Frequency of HF and Severity (MITT, LOCF)

				--Number of Moderate and Severe HF- Adjusted Change		p-Value vs	--------Daily Severity Score of HF-------- Adjusted Change		p-Value vs
Age Group	Treatment	Time Slot	No of Pairs	Mean	SE	Placebo	Mean	SE	Placebo
< 50	BZA 20 mg/CE 0.45 mg	Week 4	29	-6.15	0.81	0.042	-0.74	0.15	0.020
		Week 12	29	-8.39	0.80	0.036	-1.11	0.24	0.116
	BZA 20 mg /CE 0.625 mg	Week 4							(b) (4)
		Week 12							
	Placebo	Week 4	19	-3.79	0.99	--	-0.23	0.18	--
		Week 12	19	-6.00	0.97	--	-0.58	0.29	--
50-59	BZA 20 mg /CE 0.45 mg	Week 4	79	-5.72	0.54	<0.001	-0.48	0.08	0.003
		Week 12	79	-7.41	0.45	<0.001	-0.75	0.09	<0.001
	BZA 20 mg /CE 0.625 mg	Week 4							(b) (4)
		Week 12							
	Placebo	Week 4	33	-2.14	0.83	--	-0.03	0.12	--
		Week 12	33	-4.59	0.69	--	-0.16	0.14	--
> 59	BZA 20 mg/CE 0.45 mg	Week 4	14	-6.73	1.35	0.021	-1.10	0.25	0.011
		Week 12	14	-8.01	1.04	0.005	-1.35	0.26	0.008
	BZA 20 mg/CE 0.625 mg	Week 4							(b) (4)
		Week 12							
	Placebo	Week 4	11	-1.26	1.57	--	0.09	0.30	--
		Week 12	11	-2.63	1.21	--	-0.05	0.31	--

Source: Table 15.38, 305 CSR p.231

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on results of the single pivotal study (Study 305), once daily administration of BZA 20/CE 0.625 and BZA 20/CE 0.45 show efficacy in reducing the frequency and severity of hot flushes at 4 and 12 weeks. (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Results over the 12-week treatment period show the greatest mean decreases in symptoms (frequency and severity) occurring 5-6 weeks after treatment onset with persistence of effect through week 12. The placebo-subtracted effect appears to decrease over time due to large placebo effect over time but remains above the baseline placebo rate.

6.1.10 Additional Efficacy Issues/Analyses

The effect of BZA alone on hot flushes was not available from the current BZA/CE program but was evaluated in (b) (4) BZA monotherapy has not been shown to have efficacy in hot flush reduction. Using adverse event tabulations, the hot flush incidence in BZA 20 mg (12%) was similar to raloxifene 60 mg (11%).(Table 33). No dose-effect was seen.

Table 33: Selected Common Adverse Events Occurring in Bazedoxifene Phase 3 Clinical Trials Compared to Evista Placebo-Controlled Osteoporosis Trials (b) (4)

	Hot flushes	Leg cramps	Vaginitis	Leukorrhea	Dry mouth	Breast pain
Interim Study 301 (Phase 3 treatment of osteoporosis)						
BAZ 20 n=1886	12.0%	9.8%	4.6%	1.6%	2.3%	2.3%
BAZ 40 n=1872	12.6%	9.3%	4.0%	1.5%	0.5%	2.1%
EVISTA 60 n=1848	11.0%	9.6%	4.4%	2.1%	0.9%	2.7%
Placebo n=1885	5.6%	7.1%	5.3%	2.3%	1.2%	2.1%
Study 300 (Phase 3 prevention of osteoporosis)						
BAZ 20 n=322	20.8%	11.5%	2.5%	3.1%	2.8%	3.4%
BAZ 40 n=319	24.1%	11.6%	1.3%	0.9%	1.6%	2.8%
EVISTA 60 n=311	18.6%	10.9%	3.2%	2.6%	0.3%	2.6%
Placebo n=310	14.2%	10.3%	3.2%	2.6%	0.6%	2.6%
EVISTA treatment of osteoporosis placebo-controlled studies						
EVISTA 60 n=2557	9.7%	7.0%	*	*	*	*

	Hot flushes	Leg cramps	Vaginitis	Leukorrhea	Dry mouth	Breast pain
Placebo n=2576	6.4%	3.7%	*	*	*	*
EVISTA prevention of osteoporosis placebo-controlled studies						
EVISTA 60 n=581	24.6%	5.9%	4.3%	3.3%	*	*
Placebo n=584	18.3%	1.9%	3.6%	1.7%	*	*

*Placebo rate higher than Evista® rate or less than 2% in all treatment groups
Source: Bazedoxifene data from (b) (4) Final Study 300 Report Table ST 10-1 (pg. 623-649) and Interim Study 301 Report Table ST-10-1 (pg. 418-438); Evista® data from Evista® Prescribing Information, **ADVERSE REACTIONS** section, Table 6, revised March 19, 2001.

The indication for the treatment of moderate to severe vasomotor symptoms was based on pivotal trial 305. Significant decreases in the mean number of moderate and severe hot flushes of -6 to -8 at Weeks 4 and 12 were seen in both BZA/CE groups ($p<0.001$) with placebo-subtracted treatment differences for BZA 20/CE 0.625 and BZA 20/CE 0.45/BZA at Week 4 of (b) (4) and -3.6 hot flushes, respectively, and at Week 12 of (b) (4) and -2.7 hot flushes, respectively. This meets the Guidance criteria of > 2 hot flushes per day. There was also a significant reduction in the severity score of hot flushes (range, -0.6 to -1.2) at Weeks 4 and 12 in both BZA/CE groups ($p<0.001$) with placebo-subtracted treatment differences between -0.49 to -0.94. (b) (4)

Therefore, no loss of effect was noted. Study 303 provided supportive VMS data due to the step-down procedure used beginning with BZA 10/CE 0.625, BZA 20/CE 0.625, BZA 40/CE 0.625, then the CE 0.45 dose regimens. Using this approach, only the BZA 20/CE 0.625 showed statistical significance for number and severity of hot flushes.

In the reviewer's opinion, the magnitude of effect in reduction in hot flushes seen with BZA/CE is similar to other marketed CE/progestin preparations. Data from CE/MPA (Prempro label) show placebo-subtracted mean values of -3.2 and -1.2, at Week 4 and Week 12, respectively, for the CE 0.625/MPA 2.5 mg, and -3.63 and -1.7, respectively, at Week 4 and Week 12 for CE 0.45/MPA 1.5 mg.

6.2 Treatment of Moderate to Severe Vulvar and Vaginal Atrophy

(b) (4)

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6.3 Prevention of Postmenopausal Osteoporosis

6.3.1 Methods

The clinical program for the prevention of postmenopausal osteoporosis included two pivotal BMD studies, Study 303, a 2-year, and Study 3307, the confirmatory 1-year study. A third 1-year study with a 1 year extension, Study 304, was conducted but will be relied upon primarily for safety due to the formulation issues and decreased bioavailability compared to the to-be-marketed formulation. Mean changes in BMD at the lumbar spine at Month 24 months (Study 303) and Month 12 (3307) were the primary endpoints of interest. The sponsor is seeking to label lumbar spine and total hip results individually for Study 303 and 3307 at Months (b) (4) 12, and 24. Therefore, these studies will be presented separately.

6.3.1 Methods

Demographics

Study 303 (2-year study BMD study)

Demographic data for the entire safety population (n=3397) are summarized in Table 44. Subjects were healthy postmenopausal women, age 40 to 75 years (mean age 56.5 years). BMI ranged from 16.2 to 35.7 kg/m2 (mean 25.8 kg/m2), with approximately 59% of subjects with BMI ≥25 kg/m2. Approximately 80.8% of the subjects were White, 13.7% were Black, and 3.7% were Hispanic. The mean number of years since the last menstrual period was 8.1, and the mean age at last menstrual period was 48.9 years. Baseline characteristics were similar across treatment groups, except for maternal history of fracture (p = 0.043, Chi-Square), which was approximately 7% overall and ranged from 4% to 10% for each treatment group.

Table 44: Demographic Data, Safety Population

	Conjugated Estrogens 0.625 mg			Conjugated Estrogens 0.45 mg				
Characteristic	BZA 10 mg	BZA 20 mg	BZA 40 mg	BZA 10 mg	BZA 20 mg	BZA 40 mg	Raloxifene	Placebo
Age (years)								
N	(b) (4)			430	433	423	423	427
Mean (SD)				56.84 (5.73)	56.22 (5.80)	56.31 (5.76)	56.54 (5.72)	56.48 (6.04)
Ethnic origin								
White				346 (80.47)	351 (81.06)	327 (77.30)	341 (80.61)	340 (79.63)
Black				57 (13.26)	54 (12.47)	66 (15.60)	57 (13.48)	66 (15.46)
Hispanic				15 (3.49)	20 (4.62)	18 (4.26)	14 (3.31)	15 (3.51)
Other				12 (2.79)	8 (1.84)	12 (2.83)	11 (2.59)	6 (1.40)
BMI (kg/m^2)								
N				430	433	423	423	426
Mean (SD)				25.83 (3.36)	25.97 (3.45)	25.57 (3.46)	25.92 (3.28)	25.94 (3.54)
Years since last menstrual perio								
N				429	433	423	423	427
Mean (SD)				7.94 (5.60)	8.11 (5.70)	7.9 (5.80)	8.33 (5.83)	8.36 (5.78)
Gail index - Mean (SD)								
N				144	133	140	126	136
Relative risk				1.80 (0.84)	1.83 (0.94)	1.97 (1.91)	1.63 (0.66)	1.75 (0.95)
5-year risk				1.53 (0.76)	1.52 (0.86)	1.59 (1.28)	1.40 (0.61)	1.48 (0.88)
Baseline spine T-score								
Study groups C and D								
N				185	182	176	188	184
Mean (SD)				-1.45 (0.67)	-1.43 (0.70)	-1.49 (0.74)	-1.48 (0.73)	-1.52 (0.76)
Study groups E and F								
N				104	110	108	107	108
Mean (SD)				-0.91 (1.23)	-0.81 (1.11)	-0.81 (1.26)	-0.81 (1.10)	-0.94 (1.06)

Source: Table 8-8, p. 94, CSR 303

BMD assessment was conducted in a subset of subjects enrolled in the Osteoporosis Substudies. Baseline characteristics for the Osteoporosis Substudies - Substudy I and Substudy II, are listed in Table 45 and represents 68% of the total safety population (2315/3397). By design, subjects in Substudy 2 had more recent onset of menopause (< 5 years) and the mean years since menopause for this population was 2.99 years (compared to 11 years in Substudy I and 8 years in the main population). As a result, subjects in Substudy 2 were also younger (mean age 52 vs 56 in Substudy I) and had mean lumbar spine T-scores in normal range (-0.83 vs -1.47 in Substudy I).

Table 45: Baseline Characteristics – Osteoporosis Substudies

	All Subjects	Substudy I	Substudy II
Age (years)			
N	3397	1454	861
Mean (SD)	56.46 (5.80)	58.53 (5.58)	52.29 (3.56)
Years since last menstrual period			
N	3396	1453	861
Mean (SD)	8.10 (5.72)	11.14 (5.12)	2.99 (1.19)
Baseline spine T-score			
N	---	1453	860
Mean (SD)	---	-1.47 (0.73)	-0.83 (1.16)
Baseline systolic blood pressure >140 mm Hg			
n (%)	428 (12.60)	235 (16.16)	53 (6.16)
Baseline diastolic blood pressure >90 mm Hg			
n (%)	228 (6.71)	148 (10.18)	35 (4.07)

Source: Table 8-9, p. 95, 303 CSR

Study 3307 (1-year BMD study)

Baseline characteristics for the Osteoporosis Substudy are listed in Table 46. Subjects were mainly white (92.5%), had a mean age of 52 years (range 42-63 years), were 2.49 years post menopause (range 0.46-20 years, attributable to outliers in the placebo group), had baseline T-score -0.90 (range -2.70 to 2.65) and mean FRAX scores that would not qualify for osteoporosis treatment. No significant differences were seen between dose groups. The Osteoporosis Substudy of 3307 was similar to Subgroup II of Study 303 based on age, years since menopause, and baseline T-score.

Table 46: Baseline Characteristics – OSS Population

Characteristic	p-Value	BZA 20 mg /CE 0.45 mg (n=135)	BZA 20 mg /CE 0.625 mg (b) (4)	BZA 20 mg (n=73)	CE 0.45 mg /MPA 1.5 mg (n=70)	Placebo (n=158)	Total (n=590)
Age (year)							
N		135		73	70	158	590
Mean	0.746[a]	53.07		52.96	52.81	53.09	52.92
Standard deviation		3.13		3.36	4.04	3.23	3.37
Minimum - maximum		46.00-60.00		45.00-62.00	43.00-61.00	42.00-62.00	42.00-63.00
Ethnic origin	0.624[b]						
Hispanic or Latino		7 (5.19)		7 (9.59)	4 (5.71)	7 (4.43)	35 (5.93)
Non-Hispanic and Non-Latino		128 (94.81)		66 (90.41)	66 (94.29)	151 (95.57)	555 (94.07)
Race	0.794[d]						
White		124 (91.85)		69 (94.52)	62 (88.57)	145 (91.77)	546 (92.54)
Black or African American		8 (5.93)		4 (5.48)	6 (8.57)	9 (5.70)	33 (5.59)
Other[c]		3 (2.22)		0	2 (2.86)	4 (2.53)	11 (1.86)
Height (cm)							
N		135		73	70	158	590
Mean	0.627[a]	164.59		163.52	163.37	163.70	163.92
Standard deviation		5.88		6.09	5.91	6.31	6.23
Minimum - maximum		149.50-180.30		147.50-177.80	151.90-177.20	145.00-180.00	145.00-181.60
Weight (kg)							
N		135		73	70	158	590
Mean	0.229[a]	69.61		70.97	71.44	68.41	69.53
Standard deviation		9.74		11.31	10.32	11.14	10.65
Minimum - maximum		44.50-99.80		49.50-98.20	48.00-95.20	45.50-102.10	41.80-102.10
BMI, (kg/m2)							
N		135		73	70	158	590
Mean	0.059[a]	25.67		26.48	26.81	25.50	25.87
Standard deviation		3.17		3.50	3.91	3.68	3.65
Minimum - maximum		18.76-33.89		18.57-33.92	18.82-33.89	17.39-33.91	16.74-33.96

Characteristic	p-Value	BZA 20 mg /CE 0.45 mg (n=135)	BZA 20 mg /CE 0.625 mg (b) (4)	BZA 20 mg (n=73)	CE 0.45 mg /MPA 1.5 mg (n=70)	Placebo (n=158)	Total (n=590)
Age at last menstrual Period							
N		135		73	70	158	590
Mean	0.832[a]	51.15		51.07	50.81	50.98	50.94
Standard deviation		3.08		3.20	3.95	3.23	3.30
Minimum - maximum		42.77-58.96		41.37-60.02	40.78-58.05	38.44-58.89	38.44-60.02
Years since last menstrual period							
N		135		73	70	158	590
Mean	0.742[a]	2.42		2.43	2.49	2.63	2.49
Standard deviation		1.25		1.33	1.35	1.94	1.49
Minimum - maximum		0.51-5.41		0.55-5.31	0.53-4.97	0.53-20.87	0.46-20.87
Type of menopause							
Natural		135 (100)		73 (100)	70 (100)	158 (100)	590 (100)
Baseline T-Score							
N		135		73	70	158	590
Mean	0.558[a]	-0.91		-0.82	-0.77	-0.95	-0.90
Standard deviation		0.77		0.75	0.78	0.91	0.82
Minimum - maximum		-2.40-1.50		-2.20-0.80	-2.40-1.25	-2.60-2.65	-2.70-2.65
Frax major osteoporotic score							
N		135		73	70	158	589
Mean	0.088[a]	5.18		4.62	4.40	4.99	4.93
Standard deviation		2.55		1.79	1.80	1.80	2.17
Minimum - maximum		1.09-17.09		1.51-8.66	1.71-10.56	1.40-10.77	1.09-17.09
Missing		0		0	0	0	1
Frax hip fracture score							
N		135		73	70	158	589
Mean	0.185[a]	0.38		0.33	0.29	0.42	0.38
Standard deviation		0.38		0.35	0.34	0.42	0.40
Minimum - maximum		0.01-2.10		0.01-1.34	0.01-1.58	0.00-2.48	0.00-2.48
Missing		0		0	0	0	1

Source: Table 8-9, p.82, 3307 CSR

Subject Disposition

Study 303 (2-year study BMD study)

Summary subject status is shown in Table 47.

Table 47: Disposition – Primary Analysis Populations

	CE 0.625 mg					
	BZA 10 mg	BZA 20 mg	BZA 40 mg			
Safety Population (Dosed Subjects)	[redacted]					(b) (4)
EE Population (month 12), Endometrial Hyperplasia						
Osteoporosis Prevention I Substudy (Groups C & D)						
MITT Population, Lumbar Spine BMD						
Osteoporosis Prevention II Substudy (Groups E & F)						
MITT Population, Lumbar Spine BMD						

	CE 0.45 mg					
	BZA 10 mg	BZA 20 mg	BZA 40 mg	Raloxifene 60 mg	Placebo	Total
Safety Population (Dosed Subjects)	430	433	423	423	427	3397
EE Population (month 12), Endometrial Hyperplasia	320 (74)	335 (77)	309 (73)	298 (70)	312 (73)	2539 (75)
Osteoporosis Prevention I Substudy	186	182	176	188	184	1454
MITT Population, Lumbar Spine BMD (Groups C & D)	167 (90)	160 (88)	159 (90)	164 (87)	159 (86)	1295 (89)
Osteoporosis Prevention II Substudy	104	111	108	107	108	861
MITT Population, Lumbar Spine BMD (Groups E & F)	95 (91)	101 (91)	97 (90)	97 (91)	99 (92)	783 (91)

Safety Population = includes subjects who were randomized and took at least 1 dose of test article.
EE = efficacy evaluable (endometrial hyperplasia): includes subjects who took at least 1 dose of test article; and had endometrial biopsy readings at screening and on treatment for the specified time point, or had hyperplasia anytime prior to the time point. Subjects also had to meet other evaluability criteria and have no major protocol violations.
MITT = modified intent-to-treat (BMD, lumbar spine): includes subjects who took at least 1 dose of test article, had lumbar spine BMD values at baseline and at least 1 value on-therapy or within 60 days of last dose of test article.

Source: Table 8-2, p. 77, CSR 303

The overall discontinuation rate and reason for discontinuation were consistent across the study groups at approximately 30% (range 29.8% to 35.7%) (Table 48). Adverse events (AEs) were the most frequent reason for discontinuation. Higher numbers of AEs were seen in the BZA/CE10 groups (15%) and placebo (14.3%). Statistical significance was seen for unsatisfactory response/efficacy in the BZA40/CE 0.45, raloxifene and placebo groups. Twenty (20) subjects had their blind broken at early withdrawal or after they had completed the study and were not excluded from the analyses. One of these subjects (303-416-307430) had significant bone loss 1 month after study completion (randomized to placebo). The other 19 were due to serious unexpected AEs and needed to be unblinded in order to submit 15 day FDA reports. Two events, one report of endometrial polyp was cancelled (303-450-314317) and one report of endometrial neoplasia /endometrial polyp (303-450-317582) turned out not to meet the SAE criteria and the subject completed the study. (Reference, Appendix D.13.2).

Table 48: Number (%) of Subjects Who Discontinued Study by Primary Reason

		Treatment							
		BZA 10/CE 0.625	BZA 20/CE 0.625	BZA 40/CE 0.625	BZA 10/CE 0.45	BZA 20/CE 0.45	BZA 40/CE 0.45		
Conclusion Status Reason [a]	Overall p-Value	[redacted]		(b) (4)	n=430	n=433	n=423	Raloxifene 60 n=423	Placebo n=427
Discontinued	0.610				141 (32.8)	129 (29.8)	142 (33.6)	151 (35.7)	151 (35.4)
Adverse event	0.192				63 (14.7)	46 (10.6)	43 (10.2)	59 (13.9)	61 (14.3)
Death	0.769				0	0	1 (0.2)	0	1 (0.2)
Failed to return	0.113				14 (3.3)	18 (4.2)	24 (5.7)	22 (5.2)	13 (3.0)
Other event	0.463				26 (6.0)	22 (5.1)	25 (5.9)	22 (5.2)	19 (4.4)
Protocol violation	0.370				5 (1.2)	5 (1.2)	7 (1.7)	3 (0.7)	12 (2.8)
Subject request unrelated to study	0.886				32 (7.4)	34 (7.9)	34 (8.0)	36 (8.5)	33 (7.7)
Unsatisfactory response - efficacy	0.002**				1 (0.2)	4 (0.9)	8 (1.9)	9 (2.1)	12 (2.8)

Overall p-value: Refers to No. of Subjects data. P-value for Chi-Square.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
a. Subjects whose primary reason for discontinuation was adverse event, based on the Study Termination Record Case Report Form (CRF); data differ from those presented in Section 10.3.3, as the latter are based on the Adverse Event Record CRF and include subjects for whom the primary or secondary reason for discontinuation was adverse events.

Source: Table 8-3, p. 79 303 CSR

Study 3307 (1-year BMD study)

Summary subject status (number, %) for the Osteoporosis Substudy in Study 3307 is shown in Table 49.

Table 49: Osteoporosis Substudy -Summary of Subject Status

	BZA 20 /CE 0.45	BZA 20 /CE 0.625	BZA 20	CE 0.45 /MPA 1.5	Placebo	Total
Total Safety Population	445	(b) (4)	230	220	474	1843
Randomly assigned and dosed	135		73	70	158	590
MITT population						
Included	199 (88%)		56 (77%)	59 (84%)	139 (88%)	512 (87%)
Excluded	16 (12%)		17 (23%)	11 (16%)	19 (12%)	78 (13%)
Per Protocol (Month 12)						
Included	108 (80%)		54 (74%)	50 (71%)	125 (79%)	460 (78%)
Excluded	27 (20%)		19 (26%)	20 (29%)	33 (21%)	130 (22%)
Source: Table 8-1, p. 60, 3307 CSR						

Subject disposition for the Osteoporosis Substudy is shown in Table 49. An imbalance in the discontinuation rates was seen in the CE/MPA group (27.1%) and BZA 20 mg group (24.7%) compared to 15-18% in the remaining groups (
Table 50). Adverse events (7.3%, overall) and subject request (4.1%, overall) were the top reasons.

Table 50: Subject Disposition – N (%) Osteoporosis Substudy

Conclusion Status Reason[a]	Overall p-Value[b]	BZA 20 mg /CE 0.45 mg	BZA 20 mg /CE 0.625 mg	BZA 20 mg	CE 0.45 mg /MPA 1.5 mg	Placebo	Total
Total		135 (100)	(b) (4)	73 (100)	70 (100)	158 (100)	590 (100)
Completed	0.197	109 (80.7)		55 (75.3)	51 (72.9)	129 (81.6)	475 (80.5)
Discontinued	0.197	26 (19.3)		18 (24.7)	19 (27.1)	29 (18.4)	115 (19.5)
Adverse event	0.490	10 (7.4)		7 (9.6)	8 (11.4)	9 (5.7)	43 (7.3)
Investigator request	0.586	0		0	0	0	1 (0.2)
Lost to follow-up	0.064	1 (0.7)		3 (4.1)	3 (4.3)	0	10 (1.7)
Other	0.096	3 (2.2)		2 (2.7)	0	6 (3.8)	11 (1.9)
Protocol violation	0.450	2 (1.5)		2 (2.7)	4 (5.7)	4 (2.5)	15 (2.5)
Subject request	0.218	9 (6.7)		0	2 (2.9)	7 (4.4)	24 (4.1)
Unsatisfactory response (efficacy)	0.101	1 (0.7)		4 (5.5)	2 (2.9)	3 (1.9)	11 (1.9)

a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject;
b. P-value for 5x2 contingency table based on Chi-square test.
Abbreviations: BZA=bazedoxifene; CE=conjugated estrogens; MPA=medroxyprogesterone acetate.
Source: CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3115A1/3307/Final Reports March 18/3115-3307 CPP5_OSS 10MAR11 10:10.

Source: Table 8-3, p. 65 303 CSR

6.3.4 Analysis of Primary Endpoint: Bone Mineral Density

The ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates was utilized. The MITT was the primary analysis population for the BMD endpoints in Study 303 and Study 3307, namely, lumbar spine, total hip, femoral neck and femoral

trochanter. Distal radius measurements were performed only in Study 303 at selected study sites and data were pooled across substudies. For Study 303, the following step-down procedure was used: BZA 10/CE 0.625 was tested first, then BZA 20/CE 0.625, BZA 40/CE 0.625, then CE 0.45 doses. For Study 3307, the step-down procedure tested CE 0.625/BZA 20 first, then BZA 20/CE 0.45. Due to 8.1% of subjects with missing source documentation in Study 303, data excluding these subjects (termed the Sensitivity Analysis) will be the primary efficacy population with reference to data including subjects with missing source documentation (termed the Original Analysis). Missing documentation was not an issue in Study 3307.

Lumbar Spine Bone Mineral Density

Study 303:
Based on the sensitivity analysis (excluding subjects with missing source documentation), the placebo-subtracted least square mean change from baseline at the lumbar spine in Subgroup I (> 5 years since menopause) was (b) (4) and 3.11% for CE 0.625/BZA 20 and CE 0.45/BZA 20, respectively. These values were numerically higher than the original analysis (includes subjects with missing source documentation) of (b) (4) and 3.11%, respectively, with both analyses demonstrating statistical significance ($p<0.001$) at both doses sought for registration. For Subgroup II ($1 \leq$ Years since menopause ≤ 5), the sensitivity analysis showed placebo-subtracted mean changes from baseline at the lumbar spine of (b) (4) and 3.62% for CE 0.625/BZA 20 and CE 0.45/BZA 20, respectively, and the changes were similar to the original analysis. Greater mean changes in BMD values were seen in Substudy II compared to Substudy I suggesting more dynamic bone in those with newer onset menopause with greater bone losses in the placebo group and greater bone gains on therapy. Again, both analyses demonstrated statistical significance ($p<0.001$). See Table 51.

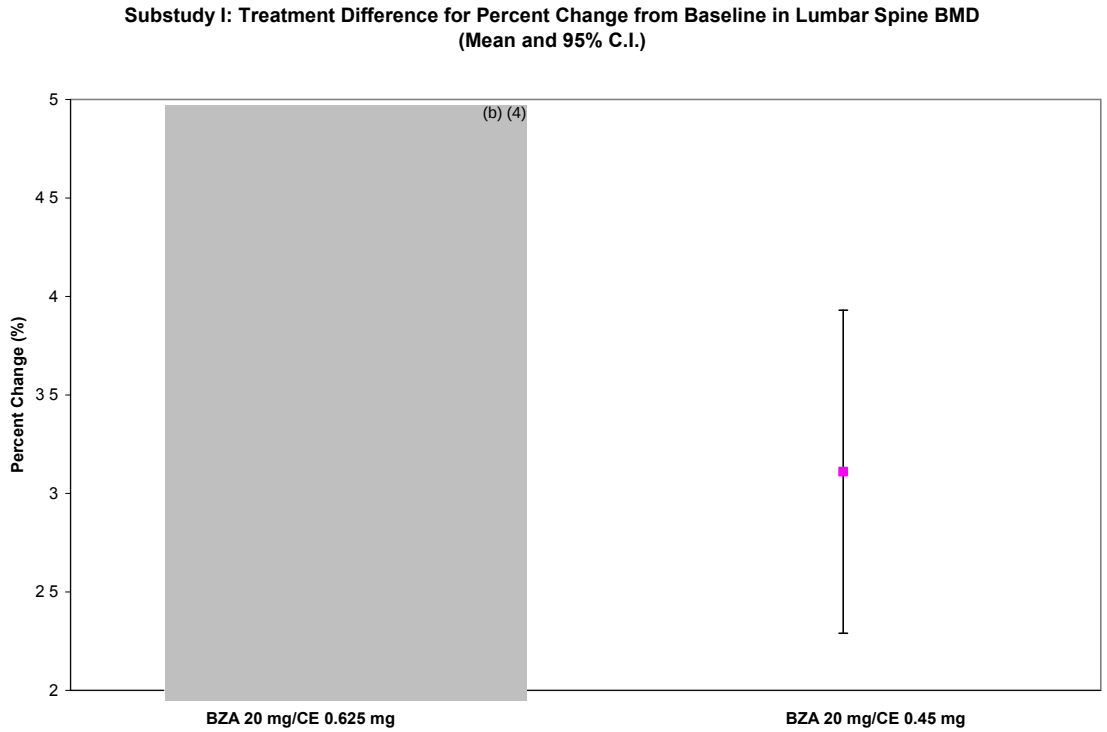
Table 51: Study 303- Lumbar Spine BMD - Treatment Difference for Percent Change from Baseline at Month 24 (Primary Efficacy Population, MITT, excluding Subjects with Missing Source Documentation [Sensitivity Analysis], LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
> 5 Years Since Menopause (Substudy I)				
BZA 20 mg/CE 0.625 mg				(b) (4)
BZA 20 mg/CE 0.45 mg	**155**	**1.64%**	**3.11% (2.29%, 3.93%)**	**< 0.001**
Raloxifene 60 mg	**157**	**0.75%**	**2.22% (1.40%, 3.04%)**	**< 0.001**
Placebo	**151**	**-1.47%**		
1 ≤ Years Since Menopause ≤ 5 (Substudy II)				
BZA 20 mg/CE 0.625 mg				(b) (4)
BZA 20 mg/CE 0.45 mg	**95**	**1.72%**	**3.62% (2.64%, 4.60%)**	**< 0.001**
Raloxifene 60 mg	**90**	**0.13%**	**2.03% (1.03%, 3.02%)**	**< 0.001**
Placebo	**95**	**-1.90%**		

Source: Statistical Reviewer's analysis.
Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

For subgroup II, no difference can be easily seen between the BZA/CE doses. For subgroup I, a small numerical difference in mean and placebo-subtracted values was seen between the two BZA/CE doses, but the confidence intervals overlap considerably suggesting no difference - Figure 5.

Figure 5: Mean Percent Change (95% CI) in Lumbar Spine BMD – Study 303 (Subgroup I)



Source: Statistical Reviewer Review

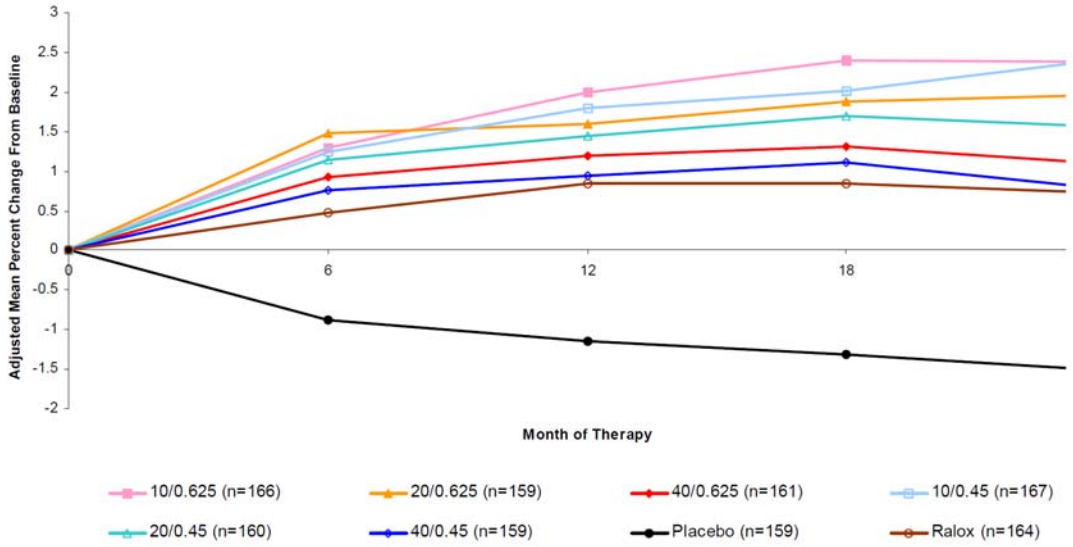
When all BZA/CE dose groups were considered, the magnitude of BMD increase was inversely related to BZA dose (Table 52). Greater mean increases in BMD were seen in the BZA 10 mg group with attenuation of effect as BZA dose increased to 40 mg. This attenuation contributes to the narrow therapeutic index seen with BZA therapy.

Table 52: Study 303 – Lumbar Spine Treatment Difference for Percent Change from Baseline at Month 24 (MITT, Sensitivity Analysis, LOCF) All Dose Groups

	n	LS Mean	LS mean Difference from placebo	p-value
Substudy I				
10 BZA/ **CE 0.625**	(b) (4)			
20 BZA/ **CE 0.625**				
40 BZA/ **CE 0.625**				
10 BZA/ **CE 0.45**	141	2.42	3.89	<0.001
20 BZA/ **CE 0.45**	155	1.64	3.11	<0.001
40 BZA/ **CE 0.45**	137	0.92	2.39	<0.001
Raloxifene	157	0.75	2.22	--
Placebo	151	-1.47	--	--
Substudy II				
10 BZA/ **CE 0.625**	(b) (4)			
20 BZA/ **CE 0.625**				
40 BZA/ **CE 0.625**				
10 BZA/ **CE 0.45**	80	2.22	4.15	<0.001
20 BZA/ **CE 0.45**	94	1.69	3.62	<0.001
40 BZA/ **CE 0.45**	82	1.30	3.23	<0.001
Raloxifene	89	0.12	2.05	--
Placebo	94	-1.93	--	--
Source: Table 1 and 2, Sponsor Information Amendment, April 9, 2013				

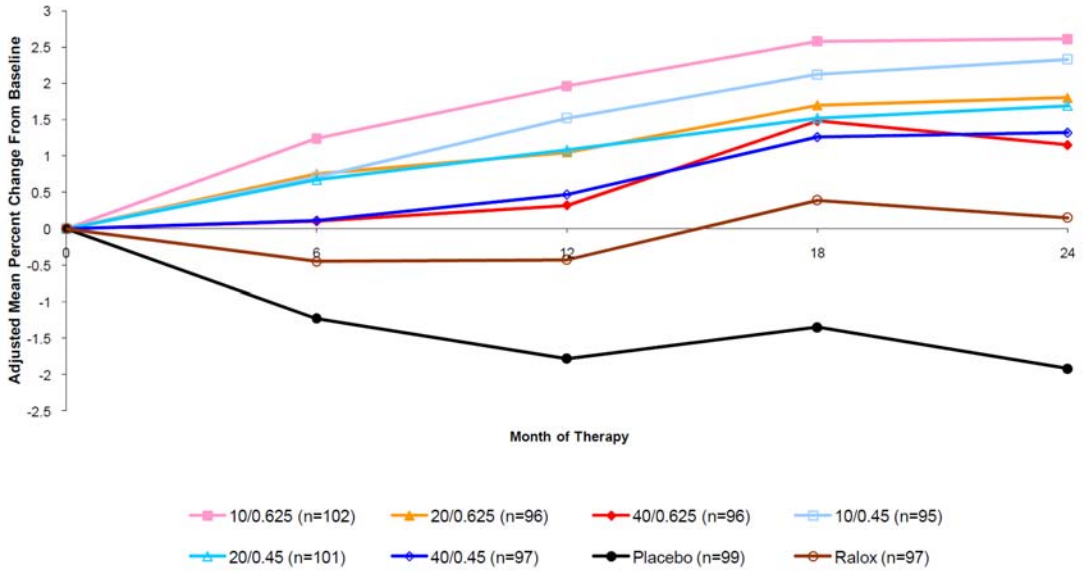
The mean change over time from baseline to Month 24 is shown in Figure 6 (Substudy I) and Figure 7 (Substudy II). For BZA 20/CE groups, the onset of BMD effect appears at 6 months with maximal effect seen by 24 months in most groups with evidence of a plateau effect.

Figure 6: BMD Lumbar Spine – Mean % Change from Baseline to Month 24 (MITT, LOCF) Substudy I



Source: Figure 9-1, p. 115, CSR 303

Figure 7: BMD Lumbar Spine – Mean % Change from Baseline to Month 24 (MITT, LOCF) Substudy II



Source: Figure 9-2, p. 116, CSR 303

Study 3307

The LS mean percent change from baseline to Month 12 at the lumbar spine are shown in Table 53. The placebo-subtracted mean change in the CE 0.625/BZA 20 and BZA 20/CE 0.45 groups was (b) (4) and 1.51%, respectively. Using the step-down procedure, statistical significance was shown for both dose groups. The CE/MPA dose was numerically greater than either BZA/CE dose combinations but there was no difference statistically.

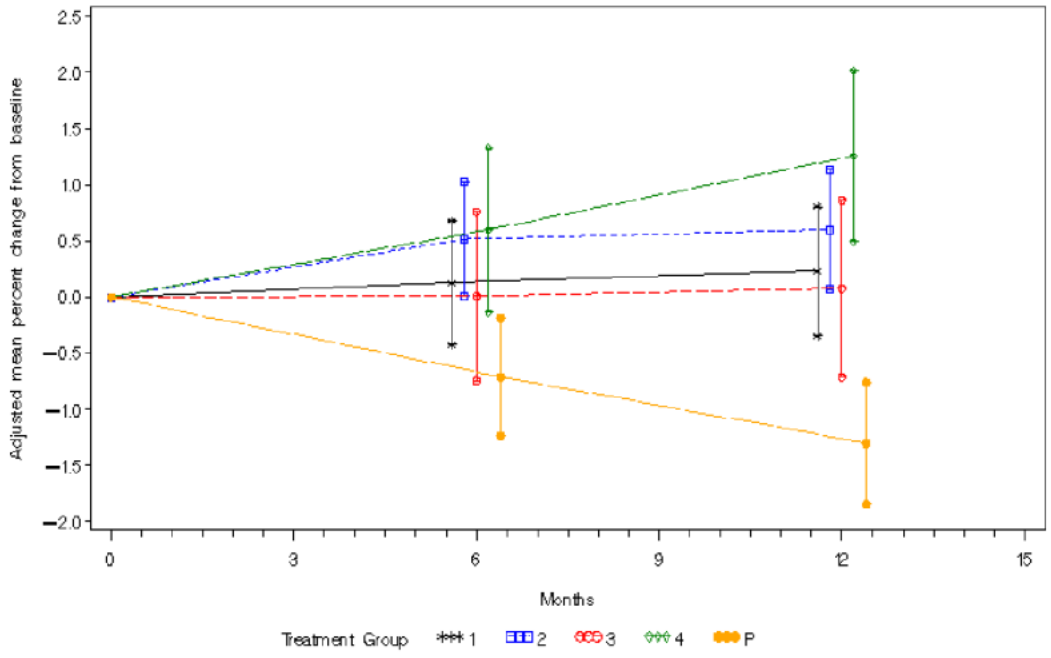
Table 53: 3307: Lumbar Spine BMD - Treatment Difference for Percent Change from Baseline at Month 12 (Primary Efficacy Population (MITT), LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
< 5 Years Since Menopause				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**119**	**0.24%**	**1.51% (0.82%, 2.20%)**	**< 0.001**
BZA 20 mg	**56**	**0.07%**	**1.34% (0.47%, 2.21%)**	**0.0026**
MPA 1.5 mg/ CE 0.45 mg	**59**	**1.30%**	**2.57% (1.72%, 3.43%)**	**< 0.001**
Placebo	**139**	**-1.28%**		

Statistical Reviewer Analysis
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates

The mean change over 12 months is shown graphically in Figure 8. Results show a relatively stable change in BZA/CE groups from Month 6 to Month 12 with progressive bone loss in the placebo group. Progressive changes were seen in the CE/MPA group. Month 12 data compared to placebo are shown again in Figure 9. All doses performed better than placebo.

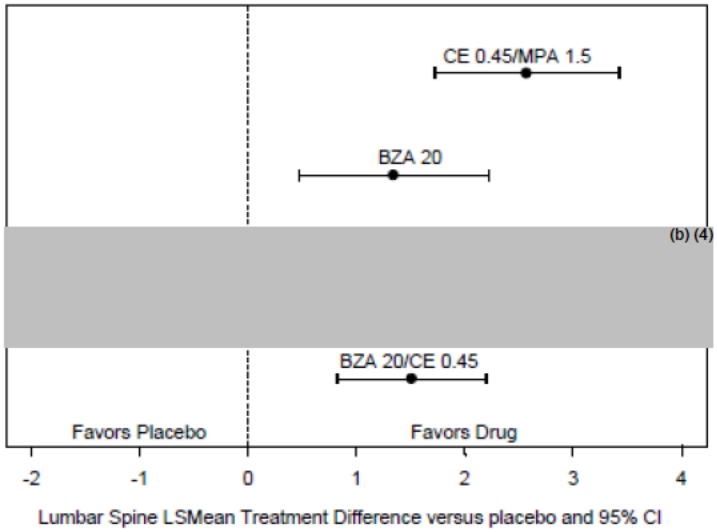
Figure 8: Study 3307 - Adjusted Mean Change – Lumbar Spine Month 6 and Month 12



1: BZA 20 mg/CE 0.45 mg 2: BZA 20 mg/CE 0.625 mg 3: BZA 20 mg
4: CE 0.45 mg/MPA 1.5 mg P: Placebo

Source: Figure 9-1, p. 102, CSR #3307

Figure 9: Study 3307 - Change from baseline in LS ANCOVA model-based comparisons to placebo



Source: Fig 9-2, p. 103, CSR 3307

Reviewer's comment: The Osteoporosis Substudy enrolled subjects in early menopause (≤5 years) with mean years since menopause approximately 2.5 years. This could explain the large decrease in BMD in the placebo group (shown in gold). The CE/MPA dose (shown in green) performed better numerically overall.

6.3.5 Analysis of Secondary Endpoints

Total Hip BMD

Study 303

The step-down procedure used for the primary analysis was not applied to secondary analyses.

Mean changes in BMD at the total hip are shown in Table 54 using the sensitivity analysis. The placebo-subtracted mean change from baseline at the total hip in Substudy I (those >5 years postmenopausal) was (b) (4) and 1.73% for CE 0.625/BZA 20 and CE 0.45/BZA 20 doses, respectively. In Substudy II (those >1 and < 5 years postmenopausal), the placebo-subtracted mean differences at the total hip were (b) (4) and 1.96% for CE 0.625/BZA 20 and CE 0.45/BZA 20 doses, respectively.

Table 54: Study 3115A1-303: Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 24 (Primary Efficacy Population (MITT) excluding Subjects with Missing Source Documentation, Sensitivity Analysis, LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
> 5 Years Since Menopause (Subgroup I)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**155**	**1.07%**	**1.73% (1.17%, 2.28%)**	**< 0.001**
Raloxifene 60 mg	**157**	**0.87%**	**1.53% (0.97%, 2.08%)**	**< 0.001**
Placebo	**150**	**-0.65%**		
1 ≤ Years Since Menopause ≤ 5 (Subgroup II)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**96**	**0.55%**	**1.96% (1.28%, 2.65%)**	**< 0.001**
Raloxifene 60 mg	**89**	**-0.31%**	**1.10% (0.40%, 1.80%)**	**0.0011**
Placebo	**95**	**-1.42%**		

Source: Statistical Reviewer's analysis and Tables 9-12 and 9-13, page 118, Study 3115A1-303 report.
Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

The original analysis showed similar results (Table 55).

Table 55: Study 303: Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 24 (Primary Efficacy Population (MITT), Original Analysis, LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
> 5 Years Since Menopause (Substudy I)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**160**	**1.06%**	**1.71% (1.16%, 2.26%)**	**< 0.001**
Raloxifene 60 mg	**164**	**0.88%**	**1.53% (0.98%, 2.08%)**	**< 0.001**
Placebo	**158**	**-0.65%**		
1 ≤ Years Since Menopause ≤ 5 (Substudy II)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**102**	**0.46%**	**1.87% (1.19%, 2.54%)**	**< 0.001**
Raloxifene 60 mg	**96**	**-0.27%**	**1.14% (0.45%, 1.82%)**	**0.0011**
Placebo	**99**	**-1.41%**		

Statistical Reviewer's analysis
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

Reviewer's comment: Both BZA/CE20 doses show efficacy at the total hip. Greater BMD improvements were seen in Subgroup I, which was different than the lumbar spine trend. (b) (4) lumbar spine and total hip results at Months 6, 12, 18, and 24. Total hip data at Month 24 may be allowed.

Study 3307

At the total hip, the placebo-subtracted mean differences were (b) (4) and 1.21% for BZA 20/CE 0.625 and BZA 20/CE 0.45 groups, respectively, at Month 12, compared to 1.19% in CE/MPA, and 1.42% in BZA 20. Statistically significance was achieved for both BZA/CE doses and BZA 20 mg alone. Comparable changes were seen between BZA/CE and CE/MPA - See Table 56.

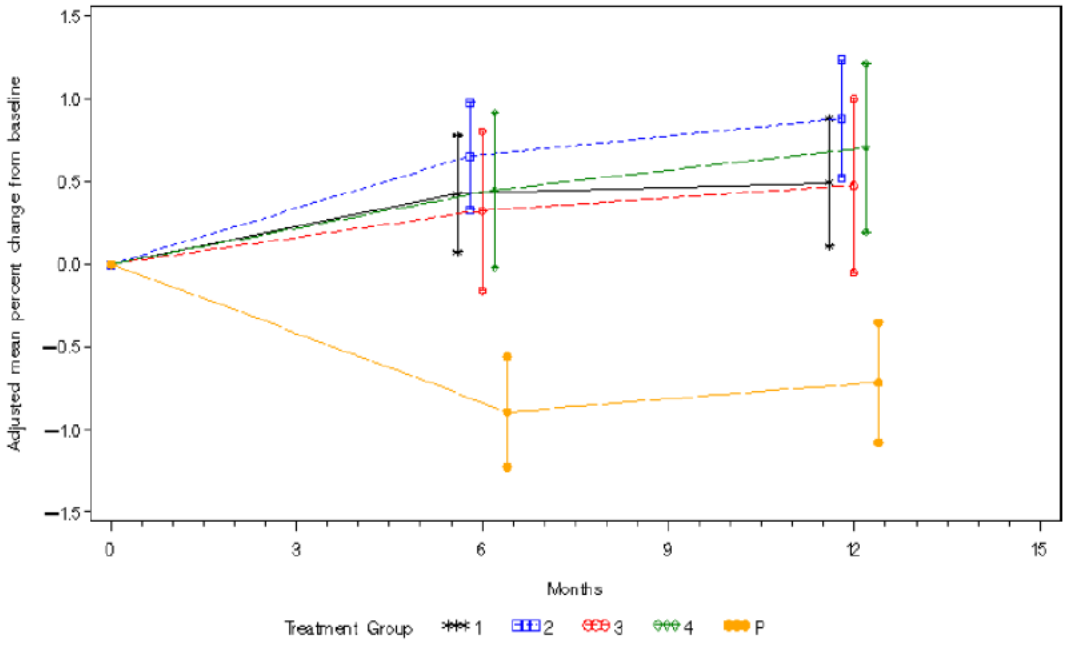
Table 56: Study 3307 - Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 12 (Primary Efficacy Population (MITT), LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
< 5 Years Since Menopause				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**119**	**0.50%**	**1.21% (0.76%, 1.67%)**	**< 0.001**
BZA 20 mg	**56**	**0.47%**	**1.19% (0.61%, 1.77%)**	**< 0.001**
CE 0.45 mg/ MPA 1.5 mg	**59**	**0.71%**	**1.42% (0.85%, 1.99%)**	
Placebo	**139**	**-0.72%**		

Statistical Reviewer's analysis
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

BMD change over time is shown graphically in Figure 7. Dose-related changes (based on the CE component) are seen over time. Month 12 data are shown again in Figure 10. Again, all doses were better than placebo.

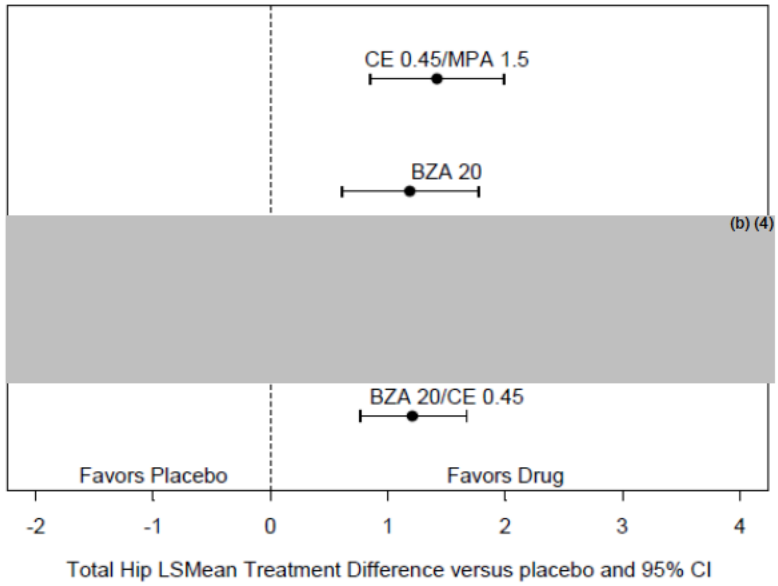
Figure 10: Percent Change from Baseline in Total Hip BMD at Month 6 and 12 (MITT, LOCF)



1: BZA 20 mg/CE 0.45 mg 2: BZA 20 mg/CE 0.625 mg 3: BZA 20 mg
4: CE 0.45 mg/MPA 1.5 mg P: Placebo

Source: Figure 9-3, p. 106, 3307 CSR

Figure 11: Change from Baseline in Total Hip ANCOVA Model-Based comparisons to placebo



Source: Figure 9-4, p. 107 CSR 3307

Femoral Neck BMD

Study 303

Based on the sensitivity analysis, the placebo-subtracted mean change from baseline at the femoral neck in Substudy I (those >5 years postmenopausal) was (b) (4) and 1.61% for BZA 20/CE 0.625 and BZA 20/CE 0.45 doses, respectively. In Substudy II (those >1 and < 5 years postmenopausal) placebo-subtracted mean differences were (b) (4) and 1.27% for BZA 20/CE 0.625 and BZA 20/CE 0.45 doses, respectively. Table 57.

Table 57: Study 303 - Femoral Neck BMD - Treatment Difference for Percent Change from Baseline at Month 24 (Primary Efficacy Population excluding Subjects with Missing Source Documentation, Sensitivity Analysis, LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
> 5 Years Since Menopause (Subgroup I)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**155**	**0.68%**	**1.61% (0.96%, 2.26%)**	**< 0.001**
Raloxifene 60 mg	**157**	**0.39%**	**1.32% (0.67%, 1.97%)**	**< 0.001**
Placebo	**150**	**-0.93%**		
1 ≤ Years Since Menopause ≤ 5 (Subgroup II)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**96**	**-0.51%**	**1.73% (0.85%, 2.61%)**	**0.0001**
Raloxifene 60 mg	**89**	**-0.97%**	**1.27% (0.38%, 2.17%)**	**0.0021**
Placebo	**95**	**-2.24%**		

Source: Statistical Reviewer's analysis.
Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

Similar results were seen in the original analysis (Table 58).

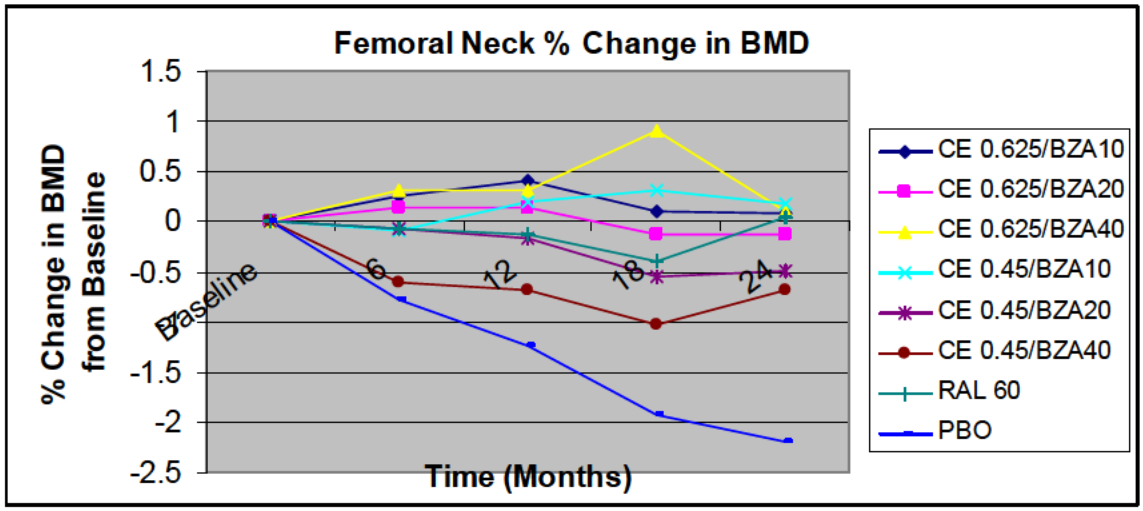
Table 58: Study 303: Femoral Neck BMD - Treatment Difference for Percent Change from Baseline at Month 24 (Primary Efficacy Population, Original Analysis, LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
> 5 Years Since Menopause (Subgroup I)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**160**	**0.65%**	**1.63% (1.00%, 2.26%)**	**< 0.001**
Raloxifene 60 mg	**164**	**0.41%**	**1.38% (0.75%, 2.01%)**	**< 0.001**
Placebo	**158**	**-0.97%**		
1 ≤ Years Since Menopause ≤ 5 (Subgroup II)				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**102**	**-0.53%**	**1.76% (0.89%, 2.63%)**	**< 0.001**
Raloxifene 60 mg	**96**	**-0.89%**	**1.40% (0.51%, 2.28%)**	**0.0021**
Placebo	**99**	**-2.29%**		

Source: Statistical Reviewer's analysis and Tables 15.46 and 15.47, pages 804 and 814, Study 3115A1-303 report.
Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model (for each subpopulation) with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

The trend of BMD attenuation with increasing BZA dose was again demonstrated across both substudies. In Substudy II, small or negative changes in BMD, compared to baseline, were seen. Within a dose, the BMD generally decreased over time (Figure 12). Bone losses of (b) (4) and -0.53% from baseline occurred in the BZA 20/CE 0.625 and BZA 20/CE 0.45 dose groups, respectively, although losses were less than losses seen with placebo (-2.29%). This bone loss likely represents the rapid decrease in BMD seen in the early phase of menopause. However, when adjusted for placebo loss, placebo-subtracted mean BMD change was (b) (4) and 1.76% for the BZA 20/CE 0.625 and BZA 20/CE 0.45 dose groups. The inverse dose-dependent trend with increasing BZA dose was again seen.

Figure 12: Femoral Neck - % Change in BMD over time –Substudy II, Original Analysis



Source: Calculated by reviewer from Table 15.47, p. 809

Study 3307

Placebo-subtracted mean changes at the femoral neck at Month 12 were (b) (4) and 0.93% for CE 0.625/BZA 20 and BZA 20/CE 0.45 groups, respectively, compared to 1.52% for CE/MPA (Table 59). Statistical significance was demonstrated for both BZA/CE doses. Statistical significance was also demonstrated in the BZA 20 mg group.

Table 59: 3307: Femoral Neck BMD - Treatment Difference for Percent Change from Baseline at Month 12 (Primary Efficacy Population, LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
< 5 Years Since Menopause				
BZA 20 mg/CE 0.625 mg	(b) (4)			
BZA 20 mg/CE 0.45 mg	**119**	**-0.07%**	**0.93% (0.33%, 1.53%)**	**0.0025**
BZA 20 mg	**56**	**0.15%**	**1.15% (0.39%, 1.91%)**	**0.0031**
MPA 1.5 mg/ CE 0.45 mg	**59**	**0.52%**	**1.52% (0.77%, 2.27%)**	**< 0.001**
Placebo	**138**	**-1.00%**		

Source: Statistical Reviewer's analysis and Table 15.32, page 910, Study 3115A1-3307 report.
Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate
* Least Squares (LS) mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment and region (U.S. or non-U.S.) as factors and baseline BMD value and years since menopause as covariates.

Femoral Trochanter BMD

Study 303

The sensitivity analysis was not performed at the femoral trochanter site and will not be labeled. Data using the original analysis are presented below.

Placebo-subtracted mean changes at the femoral trochanter for the BZA 20/CE 0.625 and BZA 20/CE 0.45 dose groups were (b) (4) and 2.13% (Substudy I) and (b) (4) and 2.16% (Substudy II) and were statistically significant (p <0.001) (Table 60). Results were similar between substudies. BMD attenuation was seen as the BZA dose increased.

Table 60: Mean Percent Change from Baseline at Month 24–Femoral Trochanter

Treatment group	N	Adjusted mean % change		p-value vs placebo	Placebo subtracted*
		Mean	SE		
Substudy I					
CE 0.625 with					
10 mg BZA	(b) (4)				
20 mg BZA					
40 mg BZA					
CE 0.45 with					
10 mg BZA	167	2.60	0.31	<0.001	2.68
20 mg BZA	160	2.05	0.31	<0.001	2.13
40 mg BZA	159	1.62	0.32	<0.001	1.70
Raloxifene	164	1.64	0.31	--	1.72
Placebo	158	-0.08	0.32	--	--
Substudy II					
CE 0.625 with					
10 mg BZA	(b) (4)				
20 mg BZA					
40 mg BZA					
CE 0.45 with					
10 mg BZA	95	2.01	0.33	<0.001	3.73
20 mg BZA	102	0.44	0.32	<0.001	2.16
40 mg BZA	95	-0.05	0.33	<0.001	1.67
Raloxifene	96	-0.09	0.26	--	1.63
Placebo	99	-1.72	0.32	--	--

*calculated by reviewer
Tables 15.46, p. 805 and Table 15.47, p.815, Original Analysis

Reviewer's comment: BZA20/CE doses show efficacy at the femoral trochanter. CE 0.625/BZA 20 had slightly higher placebo-subtracted values vs CE 0.45. No major differences were seen between substudies based on menopausal status.

Study 3307

The mean percent change in BMD at the femoral trochanter at Month 12 is shown in Table 61. Placebo-subtracted mean values for CE 0.625/BZA 20 and BZA 20/CE 0.45 groups were (b) (4) and 1.60%, respectively, compared to 1.64% for CE/MPA (calculations not shown). Statistical significance was demonstrated for both BZA/CE doses and BZA 20mg alone.

Table 61: Analysis for Femoral Trochanter (MITT, LOCF)

Analysis within and between treatment groups for BMD Femoral Trochanter (MITT, LOCF)

			--Adjusted % change--		Adjusted Difference vs. Placebo			
Treatment	Time slot	N	Mean	SE	Mean	95% CI	p-value within group	p-value vs. placebo
BZA 20 mg/CE 0.45 mg	Month 6	117	0.76	0.30	1.68	(0.967, 2.396)	0.012	< 0.001
	Month 12	119	1.31	0.31	1.60	(0.871, 2.326)	< 0.001	< 0.001
BZA 20 mg/CE 0.625 mg								(b) (4)
BZA 20 mg	Month 6	55	0.83	0.42	1.75	(0.848, 2.656)	0.047	< 0.001
	Month 12	56	1.26	0.43	1.55	(0.632, 2.474)	0.003	< 0.001
CE 0.45 mg/MPA 1.5 mg	Month 6	57	0.60	0.41	1.52	(0.632, 2.418)	0.137	< 0.001
	Month 12	59	1.35	0.41	1.64	(0.733, 2.542)	0.001	< 0.001
Placebo	Month 6	134	-0.92	0.29			0.001	
	Month 12	139	-0.29	0.29			0.321	

ancova model: percent change=treat region baseline ysm
Program: bmd_ancova . . Run on: 16DEC2010 12:37 . . Output: bmd_ML_ancova_ft.html

Source: Supplemental Table 15.32, p. 912, CSR 3307

Distal Radius BMD

Study 303

DXA of the distal radius was performed at 24 selected study sites and were pooled across both substudies (Substudy I and Substudy II). The MITT population included 312 subjects who received at least one test article dose and had both baseline and on therapy values. Mean percent change from baseline at Month 12 and Month 24 were analyzed for the ultradistal radius, 1/3 radius and total radius. Month 24 data are shown in Table 62 for the distal 1/3 radius and the ultradistal radius.

Table 62: Study 303- Mean Percent Change BMD from Baseline at Radius at Month 24 Combined Subgroups

	Radius 1/3					Ultradistal Radius				
Treatment Group	N	Adjusted Mean change		p-value vs placebo	Placebo subtracted	N	Adjusted Mean change		p-value vs placebo	Placebo-subtracted
		Mean	SE				Mean	SE		
Pooled Substudies										
CE 0.625 with										
10 mg BZA	[redacted] (b) (4)									
20 mg BZA										
40 mg BZA										
CE 0.45 with										
10 mg BZA	29	0.63	1.03	0.066	2.82	29	1.39	1.23	0.029	3.96
20 mg BZA	32	-1.49	0.99	0.631	0.70	32	-1.62	1.17	0.585	0.95
40 mg BZA	29	0.81	1.04	0.045	3.00	29	1.38	1.23	0.027	3.95
Raloxifene	32	-0.55	0.99	--	1.64	32	-2.20	1.18	--	0.37
Placebo	26	-2.19	1.12	--	--	26	-2.57	1.32	--	--
Source: Table 15.60, p. 920, 303 CSR										

Reviewer's comment: Due to the small number of subjects with radial data and the sponsor pooled the data across both substudies. Few results were statistically significant. Due to a lack of dose effect and inconsistent changes as BZA dose increased, the data are insufficient to make an assessment of the BZA/CE effect on radial BMD.

6.3.6 Other Endpoints

Bone Turnover Markers

Study 303

Serum bone turnover markers (osteocalcin and serum C-telopeptide [CTX]) were obtained in the Metabolic Substudy (also know as Osteoporosis Substudy II). Subjects were ≥1 year and ≤ 5 years postmenopausal. For BZA 20/CE groups, peak decreases in osteocalcin (max of -31%) and serum CTx (max of -55%) were seen at 12 months, indicating decreased bone turnover. [redacted] (b) (4) . All dose combinations at all time points were statistically significant compared to placebo. See Table 63.

Table 63: Bone Turnover Marker Results (Substudy II) –Median Percent Change from Baseline

			Serum Osteocalcin		Serum C-Telopeptide	
	Month	Number of Pairs[a]	Median % Change From Baseline	p-Value vs Placebo[b]	Median % Change From Baseline	p-Value vs Placebo[b]
CE 0.625 mg with:						
10 mg BZA						(b) (4)
20 mg BZA						
40 mg BZA						
CE 0.45 mg with:						
10 mg BZA	6	86	-23.93	< 0.001***	-45.73	< 0.001***
	12	79	-30.89	< 0.001***	-52.19	< 0.001***
	24	66	-22.65	< 0.001***	-45.66	< 0.001***
20 mg BZA	6	96	-27.14	< 0.001***	-40.56	< 0.001***
	12	89	-25.00	< 0.001***	-48.35	< 0.001***
	24	84	-23.09	< 0.001***	-47.78	< 0.001***
40 mg BZA	6	89	-21.90	< 0.001***	-38.45	< 0.001***
	12	81	-27.78	< 0.001***	-43.76	< 0.001***
	24	75	-20.51	< 0.001***	-42.72	< 0.001***
Raloxifene	6	89	-13.79		-25.06	
	12	81	-18.00		-33.18	
	24	66	-10.43		-35.59	
Placebo	6	96	-4.13		-6.99	
	12	84	-0.59		-4.46	
	24	73	3.08		-13.81	

a. Number of subjects with both determinations both at baseline and at the time point
b. Ranked ANCOVA; * = p<0.05; ** = p<0.01; *** = p<0.001

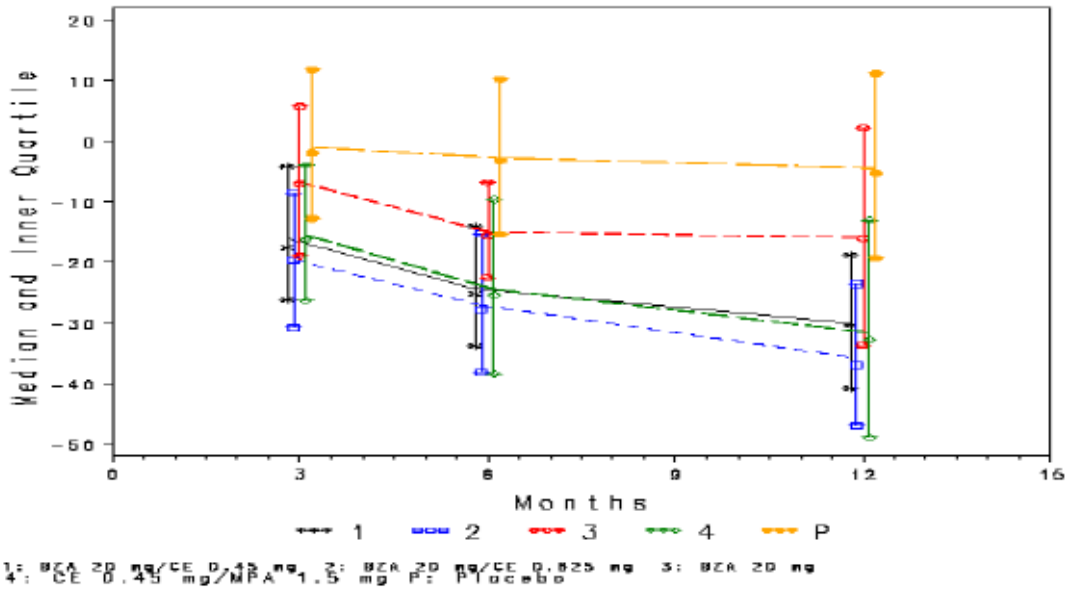
Source: Table 9-21, p. 129, 303 CSR

Reviewer's comment: From review of the dose-finding study (Study 203), the sponsor tends to present median results for bone turnover markers. It appears that bone marker data are rarely normally distributed and median data are more appropriate. (b) (4) **Bone turnover markers will not be labeled.**

Study 3307

The median percent changes from baseline in serum osteocalcin, C-telopeptide and procollagen type 1 N-propeptide (P1NP) were analyzed in the Osteoporosis Substudy. The median change from baseline in osteocalcin was (b) (4) and -30% for BZA 20/CE 0.625 (shown in blue) and BZA 20/CE 0.45 (shown in black), respectively, at Month 12 compared to placebo of -5% (shown in yellow) and CE/MPA of -33%. The nadir did not appear to have been achieved. See Figure 13.

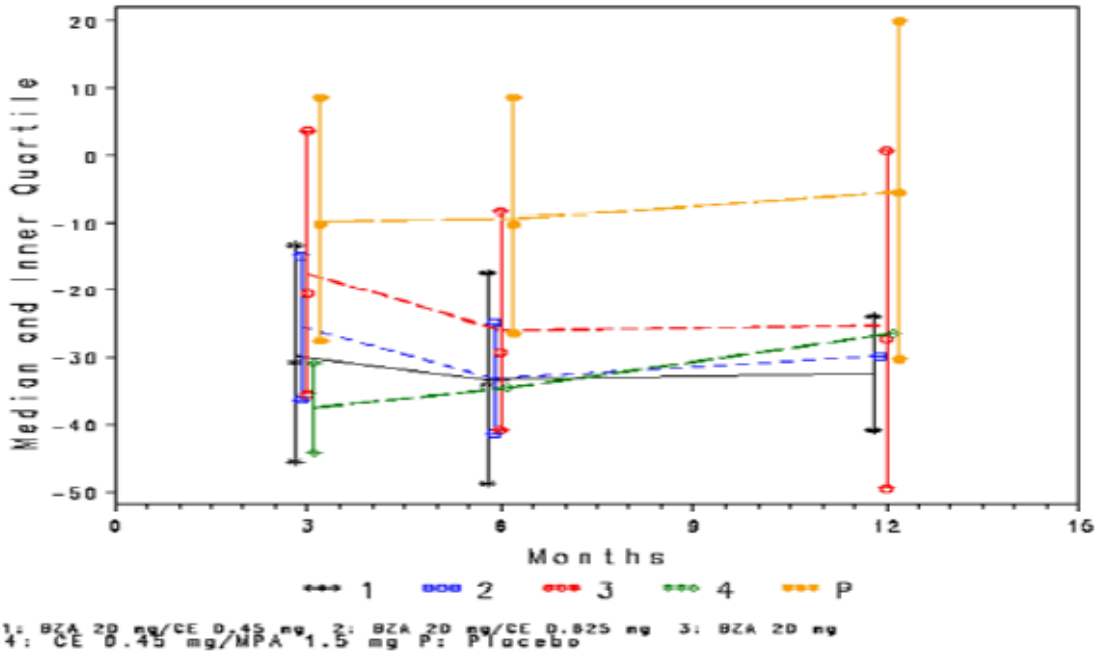
Figure 13: Change from Baseline – Osteocalcin (MITT)



Source: Fig 9-8, p. 128 CSR 3307

The median change from baseline in C-telopeptide was -(b) (4) and -41% for BZA 20/CE 0.625 (blue) and BZA 20/CE 0.45 (black), respectively, at Month 12 compared to placebo of -6% and CE/MPA of -53%. The nadir appeared at Month 6. See Figure 14.

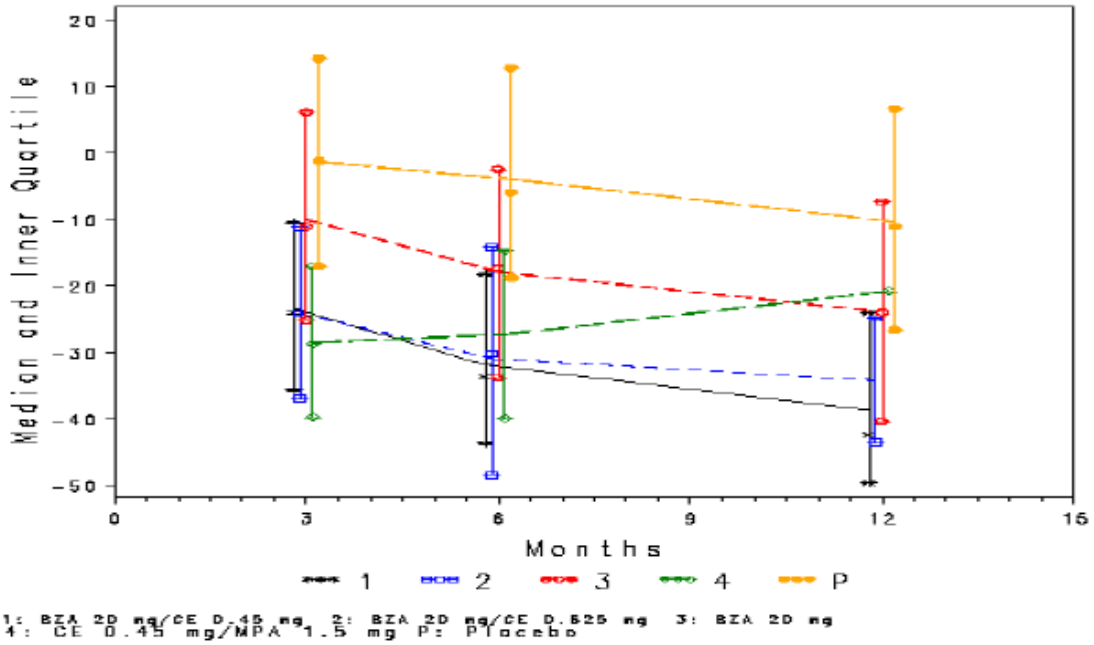
Figure 14: Change from Baseline –C-Telopeptide (MITT)



Source: Fig 9-9, p. 129 CSR 3307

The median change from baseline in P1NP was [redacted] (b) (4) and -42% for BZA 20/CE 0.625 (blue) and BZA 20/CE 0.45 (black), respectively, at Month 12 compared to placebo of -11% and CE/MPA of -50%. The nadir did not appear to have been achieved. See Figure 15.

Figure 15: Change from Baseline –P1NP (MITT)



Source: Fig 9-10, p. 130 CSR 3307

Reviewer's comment: Statistical significance in all three bone markers was seen at Month 12 when BZA 20/CE 0.45 and BZA 20/CE 0.625 were compared to placebo. Both BZA/CE doses showed decreases in bone turnover. Interestingly, bone marker results showed lesser changes from baseline in the placebo group (compared to active therapy) for both bone formation and bone resorption markers. The placebo group tended to have been menopausal slightly longer then the Osteoporosis Substudy (2.63 yrs vs 2.49 yrs), had a slightly lower mean T score (-0.95 vs -0.90), and a higher FRAX hip score (0.42 vs 0.38). None of these small differences in baseline characteristics adequately explain this trend.

Osteopenia population – Post hoc analysis

Lumbar spine:
In Study 303: In response to an Information Request to assess the effect of BZA/CE in patients with low bone mass, the sponsor submitted updated analyses of Subgroup II including only those subjects with low bone mass (-2.5 ≤ baseline T score ≤ -1) (submission dated April 9, 2013). The low bone mass group accounted for 431/773 (55%) of total population in Subgroup II (sensitivity analysis). Results of the post-hoc

BMD analysis at the lumbar spine are shown in Table 64 and are limited to proposed doses for registration and the control groups.

Table 64: Study 303 - Lumbar spine BMD - Osteopenia Subgroup (Subgroup II) at Month 24

	Pairs	Adjusted% Change from baseline		P-value vs placebo	Placebo-subtracted change
		Mean	SE		
CE 0.625/BZA 20 mg	(b) (4)				
CE 0.45/BZA 20 mg	55	2.09	0.50	<0.001	4.19
Placebo	62	-2.10	0.47	--	--
Raloxifene 60 mg	49	-0.05	0.53	--	--
Source: Table 7, p 19 of 44, Information Amendment, submitted 4/9/13					

A placebo-subtracted mean BMD change of 4.2% was seen in both BZA20/CE dose groups (compared to earlier subgroup II efficacy results of (b) (4) and 3.6% in the CE 0.625/BZA 20 and CE 0.45/BZA 20 dose groups, respectively) showing consistent results. The results also suggest an increased BMD effect in patients with osteopenia. Interestingly, no dose response was seen with respect to CE dose in the osteopenic population.

Total Hip

Results of the post-hoc BMD analysis in the osteopenic population for the total hip are shown in Table 65, and are limited to the proposed doses for registration and the control groups.

Table 65: Total Hip BMD: Osteopenia Subgroup (Subgroup II) at Month 24

	Pairs	Adjusted% Change from baseline		p-value vs placebo	Placebo-subtracted change
		Mean	SE		
CE 0.625/BZA 20 mg	(b) (4)				
CE 0.45/BZA 20 mg	55	0.78	0.34	<0.001	0.94
Placebo	62	-1.23	0.32	--	--
Raloxifene 60 mg	48	-0.16	0.36	--	--
Table 8, p 21 of 44, Information Amendment, submitted 4/9/13					

Placebo-subtracted mean BMD changes of (b) (4) and 0.94% were seen in BZA 20/CE 0.625 and BZA 20/CE 0.45 dose groups, respectively, (compared to earlier changes of (b) (4) and 1.96%, respectively, using the subgroup II population, sensitivity analysis). Smaller effects at the total hip were seen in the osteopenic population, however, statistical significance was still achieved. Interestingly, no dose response was seen with respect to CE dose in the osteopenic population.

Population Taking Concomitant Bone Active Drugs – Post hoc analysis

Study 303:
Overall, 16% of subjects were taking concomitant bone active drugs during the study. The majority of the medications had the potential to decrease rather than increase BMD. By request of the Division, the sponsor submitted datasets and summary tables (April 9, 2013) that included post hoc BMD analysis results limited to subjects taking bone active medications. The data from Subgroups I and II were combined for this analysis instead of being reported separately. Also, the original MITT analysis was used rather than the sensitivity analysis that excluded subjects with missing source documentation.

At the total hip, the placebo-subtracted BMD change using the combined subgroup was (b) (4) for the BZA 20/CE 0.625 mg group and (b) (4) for the BMD results at the BZA 20/CE 0.625 (Table 66). Data separated by subgroup (I and II) are also shown. The bone active population appeared to have a smaller BMD changes for both BZA/CE treatment groups.

Table 66: Total Hip: Change from Baseline and Placebo-Subtracted Change at Month 24 - Subjects Taking Bone Active Medication, Comparator (MIITT, LOCF)

				Comparator	
Dose	No of pairs[1]	% change from baseline	Placebo subtracted (Subgroups I, II combined)	Subgroup	Total population (placebo subtracted) Original (Sensitivity)
CE 0.625/BZA 20	(b) (4)				
CE 0.45/BZA 20	38	0.27	1.47	Combined	--
	18	0.62	1.43	Subgroup I	1.71 (1.72)
	21	-0.03	1.71	Subgroup II	1.8 (1.99)
Raloxifene	39	0.19	1.42	Combined	--
	21	0.63	1.44	Subgroup I	1.53 (1.52)
	18	-0.33	1.41	Subgroup II	-1.14 (-1.13)
Placebo	40	-1.23	--	--	--

[1]Baseline and at least one post baseline measurement
Source: Table 17 4/9/13, p. 36-37

Study 3307:
An analysis of BMD at the lumbar spine (Table 67) and total hip (Table 68) was performed in the 21 sponsor-reported subjects (a total of 23 subjects were listed in the accompanying dataset) taking bone active drugs.

Table 67: Lumbar Spine BMD – MITT (LOCF) – Osteoporosis Substudy Subjects on Bone Active Drugs

Treatment	Time	N	---------Baseline---------				---------Observed---------				% Change from Baseline	
			Min	Max	Mean	SD	Min	Max	Mean	SD	Mean	SD
BZA 20 mg/CE 0.45 mg	Month 6	6	1.01	1.43	1.12	0.16	1.00	1.43	1.12	0.16	-0.23	1.22
	Month 12	6	1.01	1.43	1.12	0.16	1.01	1.46	1.14	0.16	0.85	1.15
BZA 20 mg/CE 0.625 mg	Month 6											(b) (4)
	Month 12											
BZA 20 mg	Month 6	2	0.91	0.94	0.92	0.02	0.90	0.90	0.90	0.00	-2.36	2.02
	Month 12	2	0.91	0.94	0.92	0.02	0.91	0.95	0.93	0.03	0.65	5.45
CE 0.45 mg/MPA 1.5 mg	Month 6	3	1.20	1.36	1.29	0.08	1.18	1.34	1.26	0.08	-2.33	1.05
	Month 12	3	1.20	1.36	1.29	0.08	1.22	1.38	1.30	0.08	0.97	1.18
Placebo	Month 6	7	0.90	1.41	1.04	0.18	0.90	1.37	1.02	0.17	-1.84	1.62
	Month 12	7	0.90	1.41	1.04	0.18	0.87	1.38	1.02	0.17	-1.55	2.48

N = Number of subjects with baseline and at least one post baseline data
BZA = bazedoxifene acetate; CE = conjugated estrogens; LOCF = last observation carried forward; MITT = modified intent-to-treat;
MPA= medroxyprogesterone acetate; OSS= osteoporosis substudy; SD = standard deviation.
Source: bmd_MLB_ls

Source: Table 18, p. 38, Efficacy Amendment 4/9/13

Table 68: Total Hip BMD – MITT (LOCF) – Osteoporosis Substudy Subjects on Bone Active Drugs

Treatment	Time	N	---------Baseline---------				---------Observed---------				% Change from Baseline	
			Min	Max	Mean	SD	Min	Max	Mean	SD	Mean	SD
BZA 20 mg/CE 0.45 mg	Month 6	6	0.79	1.11	0.91	0.12	0.78	1.09	0.91	0.11	0.13	2.02
	Month 12	6	0.79	1.11	0.91	0.12	0.79	1.08	0.92	0.10	0.75	1.92
BZA 20 mg/CE 0.625 mg	Month 6											(b) (4)
	Month 12											
BZA 20 mg	Month 6	2	0.78	0.91	0.84	0.09	0.78	0.93	0.85	0.11	0.97	1.83
	Month 12	2	0.78	0.91	0.84	0.09	0.79	0.90	0.84	0.08	-0.13	1.45
CE 0.45 mg/MPA 1.5 mg	Month 6	3	0.91	1.05	0.99	0.07	0.90	1.05	0.98	0.07	-1.13	1.06
	Month 12	3	0.91	1.05	0.99	0.07	0.90	1.05	0.99	0.08	-0.73	1.17
Placebo	Month 6	7	0.75	1.21	0.90	0.15	0.73	1.18	0.89	0.15	-0.80	1.23
	Month 12	7	0.75	1.21	0.90	0.15	0.72	1.17	0.89	0.15	-1.08	2.33

N = Number of subjects with baseline and at least one post baseline data
BZA = bazedoxifene acetate; CE = conjugated estrogens; LOCF = last observation carried forward; MITT = modified intent-to-treat;
MPA= medroxyprogesterone acetate; OSS= osteoporosis substudy; SD = standard deviation.
Source: bmd_MLB_th

Source: Table 19, p. 39, Efficacy Amendment 4/9/13

The percent change in BMD from baseline from Table 67 and Table 68 were compared with prior values from the Osteoporosis Substudy population (comparisons shown in Table 69). Numeric differences were seen between groups but given the very small sample sizes, it is difficult to make any useful conclusions. Unexpectedly, when the type of medications were considered, results in the bone active subgroup were generally higher than the full OSS population.

Table 69: Percent BMD change (number of subjects) comparing the bone active subgroup and the OSS population

Dose Group	Bone active subgroup	OSS population
Lumbar spine		
CE 0.625/BZA 20	(b) (4)	
CE 0.45/BZA 20	0.85% (n=6)	0.24% (119)
CE/MPA	0.97% (n=3)	1.30% (59)
Placebo	-1.28% (n=7)	-1.28% (139)
Total Hip		
CE 0.625/BZA 20	(b) (4)	
CE 0.45/BZA 20	0.75% (n=6)	0.50% (n=119)
CE/MPA	-0.73% (n=3)	0.45% (n=59)
Placebo	-1.08% (n=7)	-0.72 (n=139)

Source: Tables 52, 55, 66 and 67, Clinical Review

Clinically Significant Bone Loss

Study 303

The critical value for BMD loss from baseline and withdrawal from the study was 6% for lumbar spine or 9% for total hip at the 12-month time point. A total of 31 subjects met these criteria. The distribution over the dose groups is shown in Table 70. The majority of outliers occurred in the placebo group (n=14).

Table 70: Subjects with Clinically Significant Decreases in BMD from Baseline

Treatment Group	Number	Subject Identification
BZA 10 mg/CE 0.625 mg BZA 20 mg/CE 0.625 mg BZA 40 mg/CE 0.625 mg		(b) (4)
BZA 10 mg/CE 0.45 mg	1	303-447-316114
BZA 20 mg/CE 0.45 mg	5	303-312-300816, 303-405-306721, 303-447-312947, 303-447-315306, 303-447-315644
BZA 40 mg/CE 0.45 mg	2	303-322-301425, 303-447-315604
Raloxifene	1	303-375-311889
Placebo	14	303-322-301430, 303-338-302456, 303-351-303266, 303-375-313307, 303-376-304870, 303-410-307073, 303-411-309812, 303-431-313729, 303-447-312750, 303-447-315785, 303-447-316167, 303-447-316266, 303-447-316336, 303-450-314277

Source: Table 9-10, p. 128

Reviewer's comment: Narratives were reviewed and available data are presented in Table 71. Outliers using the doses sought for registration are bolded and shown in the top half of the table. Placebo and raloxifene cases were not included in the table but are discussed below. For the BZA 20/CE 0.625, maximum losses were (b) (4) at the lumbar spine and hip. For the CE0.45/BZA20, maximum losses were 9.5% at the lumbar spine. Many (7) of the cases reviewed represent protocol violations where subjects were continued in the study despite having extreme

bone loss either by oversight or patient preference. It is unclear if these subjects were re-consented. Interestingly, four cases had improvement in BMD following continued treatment. Eleven of the cases (35%) were enrolled in the South American sites (#447 and #450). Only one of these 11 subjects (303-447-315056) had missing source documentation and was in the CE 0.625/BZA40 dose group.

As a quality check, placebo patient narratives extreme BMD outliers were reviewed from study 447 and 450. Bone losses ranged from -6% to -8%. As seen in the treatment groups, there were subjects with significant bone losses who were continued in the study after discussion with the investigator/sub-investigator or were classified as oversights. Several subjects discontinued due to personal preference or adverse events – chest pain, syncope, etc. There does not appear to be any bias by the investigator based on treatment group. Subjects did not appear to have been re-consented.

Table 71: Listing of Subjects with Significant Bone loss at Month 12 – selected dose groups

Subject	Age	Treatment Group	Substudy	Years since MP	Bone loss† (Site)	Month	Comment
(b) (4)							
303-312-300816	47	**BZA 20/CE 0.45**	I	5.3	-6.41% (LS)	12	Continued in Study Month 24, -4.49%
303-405-306721	49	**BZA 20/CE 0.45**	II	1.1	-7.6% (LS)	12	WD
*303-447-312947	57	**BZA 20/CE 0.45**	I	6.6	-9.5% (LS)	6	Extreme loss
303-447-315306	53	**BZA 20/CE 0.45**	I	9.7	-8.23% (LS)	12	Continued study (late notification) Month 18, -4.08% (then WD)
303-447-315644	61	**BZA 20/CE 0.45**	I	10.8	-6.1% (LS)	12	WD
(b) (4)							
303-447-316114	54	BZA10/CE 0.45	I	5.8	-7.3% (LS)	6	WD Month 9, -10.8% on f/u off drug 10% weight loss during trial
303-322-301425	60	BZA40/CE 0.45	I	10.7	-6.8% (LS)	12	Continued (oversight) and completed Month 18, -0.29% Month 24, -3.8%
303-447-315604	57	BZA40/CE 0.45	I	7.8	-6.6% (LS)	12	Continued and completed study Month 24, -9.7%

†Mean of BMD values used to calculate bone loss
#Subject discontinued from study because she refused additional endometrial biopsies
WD= withdrawn
* Extreme BMD loss
Source: Complied from narratives

Study 3307

In study 3307, five subjects had bone loss of ≥6% at the lumbar spine or ≥9% at the total hip from baseline during the study. Four of the five subjects were randomized to placebo. The narrative for the 5th subject randomized to CE 0.625/BZA 20 with bone loss of (b) (4) at the lumbar spine at Month 12 is as follows:

(b) (4)

(b) (4)

Reviewer's comment: Similar changes in the placebo group at Month 12 (7.2% (700508), 6.5% (700773), 7.9% (705957), 7.8% (706759), and 6.9% (708018) at the lumbar spine were also seen. The single on-treatment outlier is not likely to have a significant effect on interpretation of results.

6.3.7 Subpopulations

Patients who were postmenopausal < 5 years (Subgroup II) demonstrated weak or no dose effect at the lumbar spine between the two proposed doses, BZA 20/CE 0.625 and BZA 20/CE 0.45, at Month 24, however 12 month data in the same population suggested a small dose effect. For the subgroup who were menopausal for at least 5

(b) (4)

6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Daily administration of BZA 20/CE 0.625 and BZA 20/CE 0.45 demonstrated statistically significant increases in lumbar spine and total hip up to month 24. (b) (4)

6.3.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The clinical trials evaluated patients up to 24 months of therapy. The onset of BMD effect appeared at the initial 6 month time point with maximal effect seen by 24 months in most groups with evidence of a plateau effect. Longer term data is not available.

6.3.10 Additional Efficacy Issues/Analyses

To provide context for the modest maximal lumbar spine changes of (b) (4) (placebo-subtracted, (b) (4) at Month 24 following administration of BZA 20/CE 0.625, other approved products were considered. The study populations differed in mean age and entry criteria (T-score, years since menopause) but were generally healthy

postmenopausal women with at least 1 risk factor for osteoporosis. The HOPE trial (conjugated estrogen 0.625 and MPA 2.5 mg) showed greater mean changes in lumbar spine BMD of 3.28% (placebo-subtracted, 5.73%) at 2 years. Two-year data using BZA 20 monotherapy (Study 300) led to mean lumbar spine changes of only 1.41% (b) (4) While the interaction between BZA and CE is not clear, it is evident that the combination of BZA and conjugated estrogen does not exert a synergistic effect on bone. In fact, the majority of the BMD effect can be attributed to conjugated estrogen and bazedoxifene actually takes away from its effect. BZA/CE provides similar lumbar spine BMD changes as raloxifene 60 mg. In Study 303, the raloxifene 60 mg arm showed a mean LS change of 0.75% (placebo-subtracted 2.2%) which was similar to rate reported in the EVISTA label (1.8-2.4%, placebo subtracted). It is the reviewer's opinion that the BZA/CE doses provide comparable efficacy to Evista and are viable options for an alternative therapy in the prevention of osteoporosis from an efficacy perspective.

6.4 Endometrial Safety – Endometrial Protection and Endometrial Polyps

6.4.1 Study 303

Assessment for Endometrial Hyperplasia
The primary objective (and primary endpoint) of this study was to evaluate the effects of BZA/CE on the incidence of endometrial hyperplasia in postmenopausal women after 1 year of therapy. Key components of the protocol relating to endometrial protection are listed in the following bulleted items:

- Most endometrial biopsies in this study were performed at Screening, Month 6, Month 12 and Month 24. Additional endometrial biopsies were performed for prolonged or heavy uterine bleeding and if indicated by sonography. The endometrial results at Month 12 were considered primary by the Applicant. The endometrial biopsy results at 6 months and 24 months were considered secondary by the Applicant.

Reviewer's Comment: With some new molecular entities that have effects on estrogen and/or progesterone receptors it may be necessary to request longer durations of endometrial surveillance in the clinical development period. For example DBRUP encouraged one Sponsor of a progesterone receptor modulator to study endometrial protection in a 2 year study. Although a similar recommendation was not made for BZA/CE the Applicant had 2 studies (303 and 304) that provided endometrial protection data through 2 years. This reviewer feels that both time periods should be given equal weight in regard to endometrial protection.

- For this study, assessment of endometrial hyperplasia by endometrial biopsy was

used as a surrogate endpoint for endometrial cancer in accordance with the 20 March 1995 United States Food and Drug Administration (FDA) Hormone Replacement Therapy (HRT) Working Group document "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women,"

> FDA Hormone Replacement Therapy Working Group. "Guidance for clinical evaluation of combination estrogen/progestin-containing drug products used for hormone replacement therapy of postmenopausal women." 20 Mar 1995.

Reviewer's Comment: The 1995 FDA guidance document stated that endometrial biopsies should be diagnosed using standardized criteria for endometrial hyperplasia, based on Blaustein's pathology text. The 4th edition Blaustein text was released in 1994. The 4-category hyperplasia classification in this text became the endometrial hyperplasia classification that was accepted by the World Health Organization and included the following:

- **Simple hyperplasia without atypia**
- **Simple hyperplasia with atypia**
- **Complex hyperplasia without atypia**
- **Complex hyperplasia with atypia**

In 2003 the FDA issued a draft guidance for estrogen and estrogen/progestin drug products. This guidance maintained the 4-tiered classification shown above and provided an appendix with a recommended listing of histologic diagnoses to use when reading endometrial biopsies. This guidance also made a recommendation that if there was no agreement among 3 study pathologists the Applicant should apply the most severe diagnosis as the final diagnosis. This guidance also recommended that control slides containing hyperplastic changes be mixed with the study slides to help prevent bias.

In regard to study analysis the 2003 draft guidance recommended that the results from a clinical trial should demonstrate a hyperplasia rate that ≤ 1 % with an upper bound of a 1-sided 95% confidence interval that does not exceed 4 percent. The guidance also stated that the frequency of atypical hyperplasia and cancer are important additional factors to be considered in determining approvability of the drug product. The incidence of hyperplastic polyps and associated atypia should be considered in the safety review.

- The full endometrial biopsy classification used by the central pathologists for Study 303 (and similarly for Studies 304 and 3307) is shown in the following table.

Classification of Endometrial Biopsy Readings in Study 303

Classification	Readings
Endometrial malignancy	Malignancy
Hyperplasia	• Simple hyperplasia without atypia • Simple hyperplasia with atypia • Complex hyperplasia without atypia • Complex hyperplasia with atypia
Not hyperplasia	• Proliferative endometrium • Weakly proliferative endometrium • Secretory endometrium • Endometrial tissue (other = benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma) • Endometrial tissue insufficient for diagnosis • No endometrium identified • No tissue identified • Other

Source: 303 Study Report; Table 6-7; page 39 of 3915

Reviewer's Comment: Study 303 pre-dates the 2003 FDA draft guidance. The Applicant used the same classification for 2 subsequent studies (304 and 3307). Minor differences between the Applicant's classification and the FDA recommended list are shown in the following table:

Comparison of Classification Categories for Endometrial Biopsies: Studies 303, 304 and 3307 compared to the FDA 2003 Draft Guidance Recommendations

Applicant's classification (used in Studies 303, 304 and 3307	FDA 2003 recommended listing
• Endometrial tissue (other = benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma)	• Atrophic • Inactive
• Endometrial tissue insufficient for diagnosis • No endometrium identified • No tissue identified	• Tissue insufficient for diagnosis • No tissue
• Proliferative endometrium • Weakly proliferative endometrium	• Disordered proliferative endometrium • Proliferative endometrium • Weakly proliferative endometrium
• Secretory endometrium	• Secretory endometrium (cyclic type) • Secretory endometrium (progestational type – including stromal decidualization)

Source: Protocols for Studies 303, 304 and 3307; FDA 2003 Draft Guidance for Estrogen and Estrogen/Progestin Products

Reviewer's Comment: This reviewer does not feel that there are any review issues relating to the minor differences in the histologic classification.

- In Study 303, raloxifene was used as a reference for non-hyperplastic endometrial changes associated estrogen agonist-antagonist use.

- All subjects had to have an intact uterus and acceptable endometrial biopsy results at screening.

- Any subject who withdrew prematurely from the study was to have an endometrial biopsy performed if more than 3 months had elapsed since the previous assessment.

- At sites also performing transvaginal ultrasounds, if the ultrasound examination at month 12 or 24 identified non-measurable endometrium, endometrial double-walled thickness greater than 8 mm, or a focal abnormality, then hysteroscopy with directed biopsy was to be performed in place of a routine biopsy.

- In addition to the biopsies performed at the time points required per protocol, additional endometrial biopsies were to be performed for any subject who experienced prolonged or heavy uterine bleeding, or bleeding occurring more than 3 months since the last biopsy.

- All endometrial biopsies in Studies 303, 304 and 3307 were read centrally by 2 primary pathologists.

- The primary pathologists included
  - (b) (4) in Studies 303, 304 and 3307
  - (b) (4) in Studies 303, 304
  - (b) (4) in Study 3307

- Subjects were included in the study only if they had an endometrial biopsy report at screening of 1 of the following by each of the pathologists: proliferative endometrium; weakly proliferative endometrium; secretory endometrium; endometrial tissue, other (including benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc); endometrial tissue insufficient for diagnosis; no endometrium identified, or no tissue identified.

- For the on-therapy evaluations, a subject was considered to have a diagnosis of hyperplasia if both primary pathologists read hyperplasia (simple hyperplasia with or without atypia, or complex hyperplasia with or without atypia).

- If the 2 primary pathologists disagreed on the presence of hyperplasia, a third pathologist was consulted, with the final diagnosis being determined by the majority opinion.

- Secondary pathologists (who participated as the "third" pathologist included
  - (b) (4) in Studies 303, 304 and 3307
  - (b) (4) in Study 303

- An alternative definition of hyperplasia was also analyzed (based on a recommendation from FDA). For this analysis, when 3 pathologists gave disparate readings, the most severe reading was assigned as the diagnosis rather than the majority opinion.

Reviewer's Comment: Disparate readings do not apply to 2 or 3 benign (non-hyperplastic, non-malignant) diagnoses. In other words a proliferative reading is not considered disparate from weakly proliferative or inactive endometrium. An example of disparate diagnoses for 3 pathologists would be 1) atypical hyperplasia 2) complex hyperplasia and 3) benign endometrium. Atypical hyperplasia would be the most severe and thus the final diagnosis.

- Any subject having endometrial hyperplasia (based on the agreement of 2 study pathologists) was withdrawn from the study and given appropriate evaluation and treatment.

- The endometrial polyp result was to be recorded as present or not present on the endometrial biopsy by each pathologist. A diagnosis of endometrial polyp was assigned at screening or during the study if both of the primary pathologists agreed on this diagnosis. If they disagreed, a third pathologist was consulted and the final decision regarding the presence of polyp was based on the diagnosis of the majority. During screening, the histological diagnosis of endometrial polyp did not exclude a candidate from entering the study; and during the study, the histological diagnosis of endometrial polyp did not require withdrawal of the subject from the study.

Reviewer's Comment: This reviewer considers a diagnosis of hyperplastic polyp (confirmed by 2 pathologists) to equate to endometrial hyperplasia for purposes of endometrial protection endpoints.

- If more than one on-therapy biopsy exists within a timeslot, and one of the biopsies results in a diagnosis of hyperplasia, then that biopsy will be used. Otherwise, the later biopsy in the timeslot will be used in the analysis.

- At the primary time point of 1 year, an observed rate of 2% or less with an upper confidence limit of 4% or less will be considered acceptably low. (Note: This was in their original protocol)

Reviewer's Comment: DBRUP uses a point estimate of ≤ 1% with an upper one-sided 95% bound of ≤ 4%. The applicant however presented their hyperplasia data based on the current FDA recommendations.

- The primary analysis population for the incidence of endometrial hyperplasia was the efficacy evaluable (EE) population. To be included in the EE population for a given time point, subjects had to have taken at least 1 dose of test article; have an endometrial biopsy with readings by the central pathologists at screening; and have a biopsy performed on treatment for the specified time point (within 30 days before or after the time point to allow for visits not occurring precisely as scheduled); or be diagnosed with hyperplasia at any time prior to the time point.

- The EE population also had to meet the following:

    - Subjects with a reading of hyperplasia by any pathologist at baseline will be excluded from the analysis.

- Subjects must have a biopsy during month 12, or be diagnosed with hyperplasia before month 12.

- Subjects whose biopsies are taken more than 30 days after the last dose of test article will be excluded from the analysis.

Reviewer's Comment: This reviewer feels that 30 days is too short of a time period in regard to analysis exclusion

- Subjects whose biopsies are taken after another prohibited hormone medication has begun will be excluded from the analysis.

- Subjects found to have endometrial malignancy will not be included in the numerator or denominator of the incidence calculation.

Reviewer's Comment: The Applicant provided a separate analysis of hyperplasia/malignancy.

- Missing values will remain as missing.

- Subjects who have no major protocol violations. Protocol violations will be defined as:

  - Not postmenopausal

    - Postmenopausal subjects should have FSH > 30 mIU/mL, and E2 < 50 pg/mL (183.5 pmol/L) at screening;

    - Subjects who are not postmenopausal are defined as those having an FSH < 30 mIU/mL or E2 > 50 pg/mL (183.5 pmol/L) at screening.

    - Postmenopausal subjects have LNMP, if known, > 12 months prior to screening.

  - Have taken other hormones (no adequate washout; use of concomitant non-test article that may affect endometrium)

  - Have prior history of hyperplasia (before screening or during screening)

  - Have prior history of endometrial malignancy.

Endometrial Biopsy Results in Study 303

1. Benign Endometrial Diagnoses in Study 303

This reviewer evaluated the benign endometrial biopsy results for Study 303 to allow a comparison of the different doses studied. The results for the CE 0.45mg (combined with BZA 10, 20 and 30mg), raloxifene and placebo are shown in Table 72. The results are presented according to treatment, dose and individual pathologist.

Table 72: Subjects (%) with Benign Histologic Findings for Endometrial Biopsies in Study 303 (BZA 10mg, 20mg or 40mg with CE 0.45mg in Month 12) - Efficacy Evaluable Population

Diagnosis	BZA 10mg CE 0.45mg N = 320 n (%)	BZA 20mg CE 0.45mg N = 335 n (%)	BZA 40mg CE 0.45mg N = 309 n (%)	Raloxifene 60mg N =298 n (%)	Placebo N = 312 n (%)
Endometrial tissue (other)					
• Pathologist (b) (4)	213 (66.6)	278 (83.0)	272 (88.0)	266 (89.3)	272 (87.2)
• Pathologist (b) (4)	221 (69.1)	269 (80.3)	238 (77.0)	238 (79.9)	246 (78.9)
Endometrial tissue insufficient					
• Pathologist (b) (4)	14 (4.4)	11 (3.3)	12 (3.9)	14 (4.7)	23 (7.4)
• Pathologist (b) (4)	28 (8.8)	35 (10.4)	43 (13.9)	33 (11.1)	37 (11.9)
No endometrium identified					
• Pathologist (b) (4)	16 (5.0)	11 (3.3)	14 (4.5)	7 (2.3)	8 (2.6)
• Pathologist (b) (4)	25 (7.8)	15 (4.5)	25 (8.1)	23 (7.7)	23 (7.4)
No tissue identified					
• Pathologist (b) (4)	5 (1.6)	1 (0.3)	4 (1.3)	4 (1.3)	4 (1.3)
• Pathologist (b) (4)	4 (1.3)	0	2 (0.6)	1 (0.3)	1 (0.3)
Other					
• Pathologist (b) (4)	0	1 (0.3)	1 (0.3)	1 (0.3)	0
• Pathologist (b) (4)	0	2 (0.6)	0	0	0
Proliferative endometrium					
• Pathologist (b) (4)	52 (16.3)	23 (6.9)	1 (0.3)	5 (1.7)	5 (1.6)
• Pathologist (b) (4)	34 (10.6)	11 (3.3)	0	1 (0.3)	4 (1.3)
Secretory endometrium					
• Pathologist (b) (4)	0	0	1 (0.3)	0	1 (0.3)
• Pathologist (b) (4)	2 (0.6)	0	0	0	1 (0.3)
Weakly proliferative endometrium					
• Pathologist (b) (4)	20 (6.3)	11 (3.3)	4 (1.3)	4 (1.3)	1 (0.3)
• Pathologist (b) (4)	8 (2.5)	4 (1.2)	1 (0.3)	5 (1.7)	2 (0.6)

Source: Reviewer JMP analysis of dataset dbiopee in Study 303

Reviewer's Comment: The "endometrial tissue, other" category contains the most subjects. This category includes inactive and atrophic endometrium which is found in this population and would be expected if bazedoxifene inhibits proliferative endometrial changes. The inhibitory effect of BZA is dosage related as shown in both the proliferative endometrium and weakly proliferative endometrium rows in the table. The lower doses of BZA show higher numbers of proliferative and weakly proliferative endometrial tissue specimens.

The results for the CE 0.625mg (combined with BZA 10, 20 or 40mg), raloxifene and placebo are shown in Table 73. The results are presented according to treatment, dose and individual pathologist.

Table 73: Subjects (%) with Benign Histologic Findings for Endometrial Biopsies in Study 303 (BZA 10mg, 20mg or 40mg with CE 0.625mg in Month 12) - Efficacy Evaluable Population

Diagnosis	BZA 10mg CE 0.625mg	BZA 20mg CE 0.625mg	BZA 40mg CE 0.625mg	Raloxifene 60mg	Placebo
					(b) (4)
Endometrial tissue (other)					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
Endometrial tissue insufficient					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
No endometrium identified					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
No tissue identified					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
Other					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
Proliferative endometrium					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
Secretory endometrium					
• Pathologist (b) (4)					
• Pathologist (b) (4)					
Weakly proliferative endometrium					
• Pathologist (b) (4)					
• Pathologist (b) (4)					

Source: Reviewer JMP analysis of dataset dbiopee in Study 303

Reviewer's Comment: (b) (4)

2. Progestin-like or decidual-like Changes in Study 303

The comment section of the pathologist record (Section 16.2.6 Individual Efficacy and Response Data) was searched to identify histological terms related to progestin-like or decidual-like changes of the endometrial stroma. Treatment of endometrial hyperplasia with medroxyprogesterone acetate often leads to these histologic features which are characterized by a decidual-like reaction in the stroma and small atrophic appearing glands. In a decidual-like reaction stromal cells become enlarged and more epithelial-like. As seen in the following table (Table 74) the only progestin-like effects or decidual-

like effects were seen in subjects who were taking medroxyprogesterone acetate as treatment for hyperplasia. These changes were not described in subjects taking BZA/CE alone.

Table 74: Progestin-like or Decidual-like Histologic Changes in Study 303

Subject id	Age	Treatment	Study Day	Pathologist + Histologic Findings
312186	61	BZA 10mg CE 0.625mg	408	(b) (4) markedly decidualized endometrial stroma progestin effect, marked stromal decidual reaction Note: This was secondary to receiving medroxyprogesterone acetate for hyperplasia
315224	55	BZA 10mg CE 0.625mg	413	(b) (4) secretory progestin-type endometrium with pseudo decidualization Note: This was secondary to receiving medroxyprogesterone acetate for hyperplasia
315771	61	BZA 10mg CE 0.45mg	463	(b) (4) decidualized stroma progestin effect – gland atrophy – decidualized stroma Note: This was secondary to receiving medroxyprogesterone acetate for hyperplasia

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

3. Disordered Proliferative Endometrium in Study 303

Disordered proliferative endometrium is characterized by an otherwise typical proliferative endometrium with very focal cystic change and minor glandular crowding. It is not considered to be a hyperplastic process. Although this category was not included officially in the diagnosis category list for Study 303 the pathologists in the comment section often added this term. Table 75 below lists all the subjects who had at least one pathologist characterize their specimen as disordered.

Table 75: Disordered Proliferative Endometrium in Study 303

Subject id	Age	Treatment	Study Day	Pathologist + Histologic Findings
300063	55	BZA 10mg CE 0.45mg	259	(b) (4) proliferative endometrium proliferative endometrium (disordered)
	55	BZA 10mg CE 0.45mg	558	proliferative endometrium (disordered) simple hyperplasia without atypia simple hyperplasia without atypia
306060	54	BZA 10mg CE 0.45mg	716	proliferative endometrium proliferative endometrium (disordered)
306221	50	BZA 10mg CE 0.45mg	456	proliferative endometrium proliferative endometrium (disordered)
307498	60	BZA 10mg CE 0.45mg	764	proliferative endometrium proliferative endometrium (disordered)
310406	50	BZA 10mg CE 0.45mg	190	proliferative endometrium proliferative endometrium (disordered)
312078	59	BZA 10mg	358	endometrial tissue (other)

Subject id	Age	Treatment	Study Day	Pathologist + Histologic Findings
		CE 0.45mg		(b) (4) proliferative endometrium (disordered)
313733	53	BZA 10mg CE 0.45mg	353	proliferative endometrium proliferative endometrium (disordered)
314338	48	BZA 10mg CE 0.45mg	182	endometrial tissue other proliferative endometrium (disordered)
314931	54	BZA 10mg CE 0.45mg	179	proliferative endometrium proliferative endometrium (disordered)
315257	49	BZA 10mg CE 0.45mg	182	proliferative endometrium proliferative endometrium (disordered)
315682	58	BZA 10mg CE 0.45mg	717	proliferative endometrium proliferative endometrium (disordered)
315771	61	BZA 10mg CE 0.45mg	180	proliferative endometrium proliferative endometrium (disordered)
317582	52	BZA 10mg CE 0.45mg	353	proliferative endometrium proliferative endometrium (disordered)
	52	BZA 10mg CE 0.45mg	407	proliferative endometrium (disordered) proliferative endometrium
800002	66	BZA 10mg CE 0.45mg	716	proliferative endometrium proliferative endometrium (disordered)
300524	49	BZA 20mg CE 0.45mg	369	proliferative endometrium (disordered) proliferative endometrium (disordered)
303139	51	BZA 20mg CE 0.45mg	728	proliferative endometrium (disordered) proliferative endometrium (disordered)
300149	66	BZA 10mg CE 0.625mg	518	proliferative endometrium proliferative endometrium (disordered)
300644	67	BZA 10mg CE 0.625mg	363	proliferative endometrium proliferative endometrium (disordered)
301061	57	BZA 10mg CE 0.625mg	202	proliferative endometrium (disordered) proliferative endometrium (disordered)
303799	56	BZA 10mg CE 0.625mg	465	proliferative endometrium (disordered) simple hyperplasia without atypia simple hyperplasia without atypia
303850	56	BZA 10mg CE 0.625mg	340	proliferative endometrium (disordered) simple hyperplasia without atypia weakly proliferative endometrium
304359	62	BZA 10mg CE 0.625mg	729	endometrial tissue (other) focal atypical cells favor reactive etiology (b) (4) proliferative endometrium (disordered) focal surface atypia favor reactive
304765	62	BZA 10mg CE 0.625mg	490	(b) (4) proliferative endometrium (disordered) simple hyperplasia without atypia weakly proliferative endometrium
	62	BZA 10mg CE 0.625mg	714	proliferative endometrium proliferative endometrium (disordered)
304905	55	BZA 10mg CE 0.625mg	388	proliferative endometrium (disordered) simple hyperplasia without atypia endometrial tissue (other)
	55	BZA 10mg CE 0.625mg	732	proliferative endometrium proliferative endometrium (disordered)

Subject id	Age	Treatment	Study Day	Pathologist + Histologic Findings
306157	56	BZA 10mg CE 0.625mg	728	(b) (4) simple hyperplasia without atypia proliferative endometrium (disordered) weakly proliferative endometrium
306235	60	BZA 10mg CE 0.625mg	714	proliferative endometrium proliferative endometrium (disordered)
307428	66	BZA 10mg CE 0.625mg	170	endometrial tissue (other) endometrial tissue (other) (disordered)
307878	59	BZA 10mg CE 0.625mg	170	secretory endometrium proliferative endometrium (disordered)
308347	53	BZA 10mg CE 0.625mg	374	proliferative endometrium proliferative endometrium (disordered)
309165	54	BZA 10mg CE 0.625mg	344	simple hyperplasia without atypia proliferative endometrium (disordered) proliferative endometrium
	54	BZA 10mg CE 0.625mg	729	complex hyperplasia without atypia proliferative endometrium (disordered) complex hyperplasia without atypia
310520	58	BZA 10mg CE 0.625mg	99	proliferative endometrium proliferative endometrium (disordered)
312258	55	BZA 10mg CE 0.625mg	358	proliferative endometrium proliferative endometrium (disordered)
312356	61	BZA 10mg CE 0.625mg	182	simple hyperplasia without atypia proliferative endometrium (disordered) proliferative endometrium
	61	BZA 10mg CE 0.625mg	721	proliferative endometrium proliferative endometrium (disordered)
312728	57	BZA 10mg CE 0.625mg	182	endometrial tissue (other) proliferative endometrium (disordered)
314317	47	BZA 10mg CE 0.625mg	454	proliferative endometrium proliferative endometrium (disordered and eosinophilic metaplasia
314443	50	BZA 10mg CE 0.625mg	192	(b) (4) proliferative endometrium proliferative endometrium (disordered)
315224	55	BZA 10mg CE 0.625mg	178	endometrial tissue (other) proliferative endometrium (disordered)
315246	60	BZA 10mg CE 0.625mg	302	proliferative endometrium (disordered) proliferative endometrium (disordered) proliferative endometrium
315436	62	BZA 10mg CE 0.625mg	169	proliferative endometrium (disordered) proliferative endometrium (disordered)
316054	65	BZA 10mg CE 0.625mg	183	proliferative endometrium proliferative endometrium (disordered)
317323	47	BZA 10mg CE 0.625mg	375	endometrial tissue (other) proliferative endometrium (disordered)
317374	53	BZA 10mg CE 0.625mg	722	proliferative endometrium proliferative endometrium (disordered)
317495	47	BZA 10mg CE 0.625mg	356	endometrial tissue (other) weakly proliferative endometrium (disordered)

Subject id	Age	Treatment	Study Day	Pathologist + Histologic Findings
317515	50	BZA 10mg CE 0.625mg	364	(b) (4) complex hyperplasia without atypia proliferative endometrium (disordered) complex hyperplasia without atypia
305331	48	BZA 20mg CE 0.625mg	734	proliferative endometrium (disordered simple hyperplasia without atypia complex hyperplasia without atypia
300550	55	Placebo	183	proliferative endometrium proliferative endometrium (disordered)
301496	52	Placebo	355	proliferative endometrium (disordered) proliferative endometrium (disordered)

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

Reviewer's Comment: In the preceding table the study results for at least one diagnosis of disordered proliferative endometrium are the following:

- **BZA 10mg/CE 0.45mg = 16 subjects**
- **BZA 20mg/CE 0.45mg = 2 subjects**
- **BZA 10mg/CE 0.625mg =** (b) (4)
- **BZA 20mg/CE 0.625mg =**

Thus nearly all the subjects listed at least once with disordered proliferative endometrium were taking 10 mg of BZA either in combination with 0.45mg or 0.625mg of CE. As mentioned earlier disordered proliferative endometrium is not considered hyperplastic but it is often seen when there is more estrogenic influence (e.g., anovulatory cycles).

4. Endometrial Hyperplasia Cases in Study 303

The cases are described according to the 8 treatment arms (A. through H.)

A. BZA 10mg/CE 0.45mg

All the subjects in Study 303 taking BZA 10mg/CE 0.45mg with a diagnosis of endometrial hyperplasia by at least one pathologist are shown in Table 76. The light brown fill in the succeeding tables identifies those subjects who have at least 2 pathologists categorizing the biopsy as hyperplastic.

Table 76: Subjects with at least 1 Diagnosis of Endometrial Hyperplasia in Study 303 (BZA 10mg/CE 0.45mg)

Subject id	Age	Study Day	Pathologist + Histologic Findings
300063	55	183	(b) (4) proliferative endometrium simple hyperplasia without atypia weakly proliferative endometrium
		364	proliferative endometrium simple hyperplasia without atypia

Subject id	Age	Study Day	Pathologist + Histologic Findings
			(b) (4) proliferative endometrium
		383	proliferative endometrium simple hyperplasia without atypia weakly proliferative endometrium
		558	proliferative endometrium simple hyperplasia without atypia simple hyperplasia without atypia
300612	56	193	simple hyperplasia without atypia proliferative endometrium endometrial tissue (other)
300739	55	268	proliferative endometrium simple hyperplasia without atypia endometrial tissue (other)
		719	proliferative endometrium simple hyperplasia without atypia simple hyperplasia without atypia subject took DHEA from study day 428 through 646
301605	64	722	complex hyperplasia without atypia complex hyperplasia without atypia complex hyperplasia with atypia
302418	64	360	proliferative endometrium simple hyperplasia without atypia weakly proliferative endometrium
		465	proliferative endometrium simple hyperplasia without atypia endometrial tissue (other)
		731	proliferative endometrium simple hyperplasia without atypia endometrial tissue (other)
302913	53	723	weakly proliferative endometrium simple hyperplasia without atypia endometrial tissue (other)
304174	53	356	complex hyperplasia without atypia simple hyperplasia without atypia
306221	50	181	proliferative endometrium simple hyperplasia without atypia secretory endometrium
		727	simple hyperplasia without atypia simple hyperplasia without atypia
		797	complex hyperplasia without atypia complex hyperplasia without atypia
306919	53	182	proliferative endometrium simple hyperplasia without atypia proliferative endometrium
308458	57	446	proliferative endometrium simple hyperplasia without atypia weakly proliferative endometrium
312078	59	715	endometrial tissue (other) simple hyperplasia without atypia simple hyperplasia without atypia

Subject id	Age	Study Day	Pathologist + Histologic Findings
313733	53	724	(b) (4) proliferative endometrium simple hyperplasia without atypia weakly proliferative endometrium
315257	49	307	simple hyperplasia without atypia simple hyperplasia without atypia
315771	61	372	complex hyperplasia without atypia simple hyperplasia without atypia

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

Reviewer's Comment: This reviewer identified 3 subjects (304174, 315257 and 315771) with hyperplasia through Month 12. This reviewer identified 7 subjects (300063, 301605, 304174, 306221, 312078, 315257and 315771) with hyperplasia through Month 24. This reviewer concurs with the Applicant's exclusion of Subject 300739 due to concurrent use of DHEA.

B. BZA 20mg/CE 0.45mg

The cases with endometrial hyperplasia in the planned to-be-marketed dose of BZA 20mg/CE 0.45mg are shown in Table 77.

Table 77: Subjects with at least 1 Diagnosis of Endometrial Hyperplasia in Study 303 (BZA 20mg/CE 0.45mg)

Subject Id	Age	Study Day	Pathologist + Histologic Findings
300065	53	743	(b) (4) complex hyperplasia without atypia simple hyperplasia without atypia
307474	70	723	complex hyperplasia with atypia endometrial malignancy endometrial malignancy

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

Reviewer's Comment on Subject 307474:
On study day 723, **Subject 307474** had an endometrial biopsy which showed complex hyperplasia with atypia (pathologist (b) (4)), endometrial malignancy (pathologist (b) (4)) and endometrial malignancy (pathologist (b) (4)). Prior biopsies in the study for this subject were benign. The last dose of test article was taken on study day 723.

Post-study dilatation and curettage (D&C) was performed on study day 762 and showed benign endocervical tissue and small fragments of atypical endometrium suspicious for carcinoma. Post-study hysterectomy was performed on day 779. The pathology report stated that after sectioning the entire endometrium in the hysterectomy specimen, no residual atypical endometrial lesion was identified. There were 2 endometrial polyps, which appeared benign. A p53 immunostain on the larger polyp was negative.

All three pathologists considered this case to be worrisome (one diagnosis of complex hyperplasia with atypia and two diagnoses of endometrial malignancy). In addition a post-study D&C showed small fragments of atypical endometrium suspicious for carcinoma. Even though no residual atypical endometrium was identified at time of hysterectomy and a polyp did not stain for p53, this does not negate the prior findings. Based on the pathology findings this reviewer considers this to be a case of endometrial malignancy. The Applicant should mention this case in the product label.

C. BZA 40mg/CE 0.45mg

There were no cases of endometrial hyperplasia in this treatment arm.

D. BZA 10mg/CE 0.625mg

Case of endometrial hyperplasia in the BZA 10 mg/CE 0.625 mg treatment arm are shown in Table 78.

Table 78: Subjects with at least 1 Diagnosis of Endometrial Hyperplasia in Study 303 (BZA 10 mg/CE 0.625mg)

Subject Id	Age	Study Day	Pathologist + Histologic Findings
(b) (4)			

Subject Id	Age	Study Day	Pathologist + Histologic Findings
[redacted]			(b) (4)

Subject Id	Age	Study Day	Pathologist + Histologic Findings
(b) (4)			

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

Reviewer's Comment: (b) (4)

Reviewer's Comment for Subject 309325:
An endometrial biopsy for **Subject 309325** collected at 24 months (b) (6) showed endometrial malignancy (pathologist (b) (4)). The other pathologist (b) (4) read this biopsy as endometrial tissue (other). There was no record of a third pathologist for this case. Prior endometrial biopsies taken in the study were all benign.

The subject followed up with her private doctor. Comments from the medical monitor indicated that the subject had a transvaginal ultrasound performed (b) (6) which showed an endometrial thickness measuring 4.4 mm and an intramural leiomyomata. A hysteroscopy with dilatation and curettage (D&C) was performed (b) (6). Hysteroscopy revealed a symmetrical uterine cavity lined with atrophic endometrium. The endocervical curettings showed an endocervical polyp, endocervical and squamous mucosa with mild chronic inflammation, negative for dysplasia, hyperplasia, and malignancy. Endometrial curettings showed fragments of benign polyp with endometrial and endocervical characteristics, inactive endometrium with stromal breakdown and no evidence of hyperplasia or malignancy.

This reviewer considers this case to be benign based on the follow up information. There should have been a third pathologist assigned to this case.

E. BZA 20mg/CE 0.625mg

(b) (4)

F. BZA 40mg/CE 0.625mg

(b) (4)

G. Raloxifene 60mg

There were no cases of hyperplasia in the Raloxifene 60 mg treatment arm in Study 303.

H. Placebo

There were no cases of endometrial hyperplasia/neoplasia in the Placebo arm of Study 303 in which 2 pathologists concurred. The cases where one pathologist [redacted] found abnormalities are shown in Table 81.

Table 81: Subjects with at least 1 Diagnosis of Endometrial Hyperplasia in Study 303 (Placebo)

Subject Id	Age	Study Day	Pathologist + Histologic Findings
304804	65	357	[redacted] endometrial tissue (other) -- with floater of GI origin endometrial malignancy endometrial tissue insufficient for diagnosis
304823	70	720	endometrial tissue (other) complex hyperplasia with atypia endometrial tissue (other)

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

Reviewer's Comment on Subject 304804:
Subject 304804 had an endometrial biopsy at 12 months [redacted] which showed endometrial malignancy (pathologist [redacted]), endometrial tissue, other (pathologist [redacted]) and endometrial tissue insufficient for diagnosis (pathologist [redacted]).

On (b) (6) the subject underwent a hysteroscopy with a D&C. The endocervical curettage showed fibrinopurulent material with acute inflammation; no endocervical glandular tissue identified. The endometrial curettage showed fragments of endometrium, abundant hemorrhage, fibrinopurulent material, fragments of endocervical squamous mucosa, benign. No malignancy was identified in either of the tissue specimens.

On (b) (6) an endometrial biopsy was performed and showed weakly proliferative endometrium by one pathologist and proliferative endometrium by the other pathologist.

The subject completed the study and the last dose of test article was taken (b) (6) Endometrial biopsy at 24 months (b) (6) showed endometrial tissue (other) by two pathologists.

This reviewer considers this case to be benign. One of the pathologists identified a "floater" in this case. Floaters represent tissue from another source that remain in the tissue water path and periodically end up on a slide. Floaters can be identified based on the fact that only one slide contains the extraneous tissue or because the "floater" tissue is not expected. In this case it is highly unlikely for gastrointestinal tissue to be present in the specimen.

5. Endometrial Hyperplasia Incidence in Study 303

The incidence of endometrial hyperplasia through 12 months in Study 303 is shown in Table 82.

Table 82: Incidence of Endometrial Hyperplasia through Month 12 in Study 303 – Efficacy Evaluable Population

Treatment Group (a)	N	n	Incidence of Hyperplasia (%)	Confidence Interval 95% 1-S	Confidence Interval 97.5% 1-S
BZA 40mg/CE 0.45mg	309	0	0.00	0.00-0.96	0.00-1.19 (b)
BZA 20mg/CE 0.45mg	335	0	0.00	0.00-0.89	0.00-1.10 (b)
BZA 10mg/CE 0.45mg	320	3	0.94	0.26-2.41	0.19-2.72
BZA 40mg/CE 0.625mg	(b) (4)				
BZA 20mg/CE 0.625mg					
BZA 10mg/CE 0.625mg					
Raloxifene 60mg	298	0	0.00	0.00-1.00	0.00-1.23
Placebo	312	0	0.00	0.00-0.96	0.00-1.18

N = number of subjects with biopsies available at Month 12 plus all subjects with hyperplasia prior to month 12; n = number of subjects with hyperplasia at any time during the study up to and including Month 12
(a) = treatment groups are listed in order of testing per the step-down procedure used to correct for the multiplicity of comparisons (6 treatment groups)
(b) prespecified 1-sided 97.5% confidence interval per stepwise procedure to adjust for multiple comparisons was used for these 2 dosage levels
Source: Study Report 303 page 682 of 3915 (Table 15.24)

The incidence of endometrial hyperplasia through 24 months in Study 303 is shown in Table 83.

Table 83: Incidence of Endometrial Hyperplasia/Neoplasia at Month 24 in Study 303 – Efficacy Evaluable Population

Treatment Group	N	n	Incidence of Hyperplasia (%)	Confidence Interval 95% 1-S	Confidence Interval 97.5% 1-S
BZA 40mg/CE 0.45mg	268	0	0.00	0.00-1.11	0.00-1.37
BZA 20mg/CE 0.45mg	293	2	0.68		
BZA 10mg/CE 0.45mg	277	7	2.53	1.19-4.69	1.02-5.14
BZA 40mg/CE 0.625mg	(b) (4)				
BZA 20mg/CE 0.625mg					
BZA 10mg/CE 0.625mg					
Raloxifene 60mg	261	0	0.00	0.00-1.14	0.00-1.40
Placebo	259	0	0.00	0.00-1.15	0.00-1.41

N = number of subjects with biopsies available at Month 12 plus all subjects with hyperplasia prior to month 24; n = number of subjects with hyperplasia at any time during the study up to and including Month 24
Source: Study Report 303 page 682 of 3915 (Table 15.24)

Reviewer's Comment: This reviewer included 2 cases (1 case of hyperplasia and 1 case of malignancy) for the BZA 20mg/CE 0.45 mg group for an incidence of 0.68% for the Month 24 results. At both Month 12 and Month 24 the endometrial hyperplasia/neoplasia incidence was < 1.0% for the to-be-marketed doses. The upper limit of the one-sided 95% confidence interval was also <4.0.

Endometrial Polyps in Study 303

The incidence of endometrial polyps in scheduled endometrial biopsies (confirmed by at least 2 pathologists) is shown in Table 84.

Table 84: Incidence of Endometrial Polyps

Treatment Group	Month	N	n	Incidence	p-Value vs Placebo
BZA 40mg/CE 0.625mg	Screen				(b) (4)
	12				
	24				
BZA 20mg/CE 0.625mg	Screen				
	12				
	24				
BZA 10mg/CE 0.625mg	Screen				
	12				
	24				
BZA 40mg/CE 0.45mg	Screen	430	13	3.02	0.257
	12	312	3	0.96	1.000
	24	271	4	1.48	1.000
BZA 20mg/CE 0.45mg	Screen	433	9	2.08	0.801
	12	337	11	3.26	0.116
	24	300	17	5.67	0.012*
BZA 10mg/CE 0.45mg	Screen	423	14	3.31	0.127
	12	324	7	2.16	0.545
	24	279	10	3.58	0.176
Raloxifene 60mg	Screen	423	11	2.60	
	12	301	3	1.00	
	24	264	4	1.52	
Placebo	Screen	427	7	1.64	
	12	317	4	1.26	
	24	264	4	1.52	

* = p<0.05; ** = P<0.01
Source: Study 303; page 2765 of 3915

Reviewer's Comment: The Applicant stated that among the BZA/CE treatment groups there were no clear dose trends in the prior table. The only statistical difference in the to-be-marketed doses was in the BZA 20mg/CE 0.45mg at 24 months.

Polyps can be difficult to diagnose in routine endometrial biopsies because you are often dealing with fragments. Hysteroscopy is somewhat better in that it allows the gynecologist to actually visualize polyps and remove them. The Individual Efficacy and Response Data (16.2.6) allows a search for hysteroscopic directed biopsies. This reviewer identified those subjects and recorded those who had two pathologists agree on the presence of a polyp (Individual subjects listed in Table 85. These results are different from the Applicant who listed all polyps base on at least 1 pathologist.

Table 85: Subjects with Polyps (Agreed Upon by Two Pathologists)

Subject Id	Age	Rx	Study Day	Pathologist + Histologic Findings
315257	49	BZA 10mg / CE 0.45mg	388	(b) (4) endometrial polyp not present endometrial polyp present endometrial polyp present
310403	53	BZA 20mg / CE 0.45mg	378	endometrial polyp present endometrial polyp present
310403	53	BZA 20mg / CE 0.45mg	794	endometrial polyp present endometrial polyp present
304905	55	BZA 10mg / CE 0.625mg	388	endometrial polyp not present endometrial polyp present endometrial polyp present
312186	61	BZA 10mg / CE 0.625mg	422	endometrial polyp present endometrial polyp present
312186	61	BZA 10mg / CE 0.625mg	499	endometrial polyp present endometrial polyp present
315246	60	BZA 10mg / CE 0.625mg	302	endometrial polyp not present endometrial polyp present endometrial polyp present
317495	47	BZA 10 mg / CE 0.625 mg	785	endometrial polyp present endometrial polyp present endometrial polyp present
317515	50	BZA 10mg / CE 0.625mg	364	endometrial polyp not present endometrial polyp present endometrial polyp present
308356	58	BZA 20mg / CE 0.625 mg	694	endometrial polyp present endometrial polyp present
312505	54	BZA 20 mg / CE 0.625mg	367	endometrial polyp present endometrial polyp present
304908	53	BZA 20mg / CE 0.625mg	401	endometrial polyp present endometrial polyp present
304891	54	BZA 40mg / CE 0.625mg	364	endometrial polyp present endometrial polyp present
313739	53	BZA 40mg / CE 0.625mg	479	endometrial polyp present endometrial polyp present

Reviewer's Comment: The results per treatment arm from the prior table are incorporated into Table 86

Table 86: Polyps Identified Diagnosed by at least 2 Pathologists after Hysteroscopy Directed Biopsy in Study 303

Treatment group	Number of subjects
BZA 40mg/CE 0.625mg	(b) (4)
BZA 20mg/CE 0.625mg	
BZA 10mg/CE 0.625mg	
BZA 40mg/CE 0.45mg	0
BZA 20mg/CE 0.45mg	2
BZA 10mg/CE 0.45mg	1
Raloxifene 60mg	0
Placebo	0

Source: Reviewer's analysis of Individual Efficacy and Response Data

6.4.2 Study 304

Assessment for Endometrial Hyperplasia

Key components of the study in regard to endometrial biopsies and assessment for hyperplasia and polyps are found in the following bulleted items:

- The 2 primary efficacy endpoints in this study were the incidence of endometrial hyperplasia after 1 year of therapy and the mean percentage change from baseline in the BMD of the lumbar spine after 1 year of therapy compared with placebo (only for subjects participating in the osteoporosis substudy).

Reviewer's Comment: Study 304 had a 1-year extension. As noted by this reviewer in Study 303 -- if an Applicant submits endometrial biopsy data for a 2 year time period this reviewer views an endometrial hyperplasia rate >1% through Month 24 to be as clinically significant as it is through Month 12.

- The endometrial assessment was very similar to Study 303 except for the following:

    - The subject was excluded from study participation if both pathology readings were endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified.

Reviewer's Comment: This statement was present in Study 304 but not in Study 303. This reviewer does not feel that this exclusion in Study 304 impacted the effectiveness of the endometrial protection evaluation. Many subjects in this age range may have little tissue on an endometrial biopsy but yet will have an endometrial lining that is responsive and adequate to evaluate hormonal regimens. It is likely that some subjects were thus excluded who would have been good study candidates.

    - To prevent bias by the pathologists, slides showing endometrial hyperplasia

were incorporated into the batches of the study slides provided to the pathologists. These slides were incorporated before evaluation by the pathologists and were identical in size, shape, and appearance.

Reviewer's Comment: This bias prevention technique was not reported in Study 303. DBRUP incorporated this recommendation in a guidance at a point later than the Study 303 start.

Endometrial Biopsy Results in Study 304

1. Benign Endometrial Diagnoses in Study 304

This reviewer reviewed the benign endometrial biopsy results for Study 304 (Table 87). The results are presented according to treatment, dose and individual pathologist.

Table 87: Subjects (%) with Benign Histologic Findings for Endometrial Biopsies in Study 304 at Month 12

Diagnosis	BZA 20mg CE 0.45mg N = 261 n(%)	BZA 20mg CE 0.625mg (b) (4)	MPA 1.5mg CE 0.45mg N = 119 n(%)	Placebo N =135 n(%)
Endometrial tissue (other)				
• Pathologist MC	174 (66.7)		84 (70.6)	110 (81.5)
• Pathologist ITY	169 (64.8)		72 (60.5)	71 (52.6)
Endometrial tissue (insufficient/dx)				
• Pathologist MC	12 (4.6)		4 (3.4)	6 (4.4)
• Pathologist ITY	63 (24.1)		31 (26.1)	51 (37.8)
No endometrium identified				
• Pathologist MC	19 (7.3)		10 (8.4)	9 (6.7)
• Pathologist ITY	22 (8.4)		11 (9.2)	13 (9.6)
No tissue identified				
• Pathologist MC	9 (3.4)		4 (3.4)	7 (5.2)
• Pathologist ITY	2 (0.8)		2 (1.7)	1 (0.7)
Other				
• Pathologist MC	0		0	0
• Pathologist ITY	0		0	0
Proliferative endometrium				
• Pathologist MC	18 (6.9)		9 (7.6)	0
• Pathologist ITY	5 (1.9)		5 (4.2)	0
Secretory endometrium				
• Pathologist MC	1 (0.4)		0	0
• Pathologist ITY	0		0	0
Weakly proliferative endometrium				
• Pathologist MC	29 (11.1)		13 (10.9)	3 (2.2)
• Pathologist ITY	4 (1.5)		4 (3.4)	0

Source: JMP analysis of dataset dbiopee in Study 304

Reviewer's Comment: (b) (4)

2. Disordered Proliferative Endometrium in Study 304

Disordered proliferative endometrium is characterized by an otherwise typical proliferative endometrium with very focal cystic change and minor glandular crowding. Although this category was not included officially in the category list for Study 304 the pathologists in the comment section often added this term. In Table 88 below all the subjects who had at least one pathologist characterize their specimen as disordered are included.

Table 88: Disordered Proliferative Endometrium in Study 304

Subject id	Age yrs	Treatment	Study Day	Pathologist + Diagnoses
401909	53	BZA 20mg CE 0.45mg	353	(b) (4) endometrial tissue (other) proliferative endometrium (disordered)
403353	57	BZA 20mg CE 0.45mg	350	proliferative endometrium (disordered) proliferative endometrium
404628	51	BZA 20mg CE 0.45mg	362	proliferative endometrium (disordered) proliferative endometrium

(b) (4)

Source: Listing of endometrial biopsy results Study 304 Section 5.3.5.1.21

Reviewer's Comment: In the preceding table at least one Pathologist diagnosed a disordered proliferative pattern in subjects taking the following BZA/CE study drugs

- **BZA 20mg/ CE 0.45mg = 3 subjects**
- **BZA 20mg/ CE 0.625mg = (b) (4) subjects**

3. Endometrial Hyperplasia Cases in Study 304

The cases are described according to the 4 treatment arms (A. through D.)

A. BZA 20mg/CE 0.45mg

All the subjects in Study 304 taking BZA 20mg/CE 0.45mg with a diagnosis of endometrial hyperplasia by at least one pathologist are shown in Table 89.

Table 89: Hyperplasia in 304 (BZA 20mg/CE 0.45mg)

Subject Id	Age	Study Day	Pathologist + Histologic Findings
401909	53	373	(b) (4) endometrial tissue (other) simple hyperplasia without atypia + hyperplastic polyp weakly proliferative endometrium
404567	62	356	endometrial tissue (other) complex hyperplasia without atypia endometrial tissue (other)
405845	52	330	endometrial tissue (other) endometrial malignancy weakly proliferative endometrium
401662	49	732	no endometrium identified complex hyperplasia with atypia no endometrium identified
		769	endometrial tissue insufficient for diagnosis endometrial tissue (other)

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

Reviewer's Comment on Table Results: There was no concurrence of two pathologists for a diagnosis of hyperplasia in the BZA 20 mg/ CE 0.45 mg treatment arm through 24 months.

Reviewer's Comment on Subject 405845:
Subject 405845 entered the study with a screening transvaginal ultrasound (TVU) showing an endometrial thickness of 1.5 mm. The screening endometrial biopsy result showed endometrial tissue (other) by both pathologists.

On study day 330, TVU scan showed endometrial thickness of 1.7 mm. Results from the endometrial biopsy that was performed on the same day showed endometrial tissue (other) by pathologist (b) (4) endometrial malignancy ("well differentiated adenocarcinoma") by pathologist (b) (4) and weakly proliferative endometrium by pathologist (b) (4)

The subject completed year 1 of the study and entered into the study extension. The subject subsequently discontinued study medication on study day 364 and discontinued

from the study because of the abnormal endometrial biopsy results.

Forty-two (42) days after the last dose of test article, she underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. The pathology report showed that the cervix and uterus were free of lesion. The evaluation of the endometrium showed areas of proliferative endometrium and areas of atrophic endometrium without any evidence of endometrial malignancy.

Pathologist (b) (4) was the only pathologist to read neoplasia for this subject.

B. BZA 20mg/CE 0.625mg

(b) (4)

(b) (4)

Reviewer's Comment on Preceding Table: (b) (4)

Reviewer's Comment on Subject (b) (4)

Reviewer's Comment on Subject (b) (4)

(b) (4)

[redacted]

Reviewer's Comment on Subject (b) (4)

[redacted]

C. MPA 1.5mg/CE 0.45mg

All the subjects in Study 304 taking MPA 1.5 mg/CE 0.45 mg with a diagnosis of endometrial hyperplasia by at least one pathologist are shown in Table 91.

Table 91: Hyperplasia in 304 MPA 1.5mg/CE 0.45mg

Subject Id	Age	Study Day	Pathologist + Histologic Findings
404056	58	376	(b) (4) = endometrial tissue (other) and hyperplastic polyp without atypia (b) (4) = complex hyperplasia without atypia and hyperplastic polyp without atypia (b) (4) = weakly proliferative endometrium
402888	47	735	(b) (4) = proliferative endometrium (disordered) (b) (4) = simple hyperplasia without atypia (b) (4) = proliferative endometrium

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

D. Placebo

The subject in Study 304 taking placebo with a diagnosis of endometrial hyperplasia by at least one pathologist is shown in Table 92.

Table 92: Hyperplasia in 304 Placebo

Subject Id	Age	Study Day	Pathologist + Histologic Findings
401499	54	357	(b) (4) = endometrial tissue (other) (b) (4) = simple hyperplasia with atypia (b) (4) = endometrial tissue (other)

Source: Section 16.2.6 Individual efficacy and response data; Section 5.3.5.1.21

4. Endometrial Hyperplasia Incidence in Study 304

The incidence of endometrial hyperplasia through 12 months in Study 304 is shown in Table 93.

Table 93: Incidence of Endometrial Hyperplasia through Month 12 in Study 304 – Efficacy Evaluable Population

Treatment Group (a)	N	n	Incidence of Hyperplasia (%)	95% Confidence Interval UL 1-S
Applicant's Proposed Incidence				
BZA 20mg / CE 0.45mg	261	0	0.00	1.14
BZA 20mg / CE 0.625mg	(b) (4)			
MPA 1.5mg / CE 0.45mg	119	0	0.00	2.49
Placebo	135	0	0.00	2.19
Clinical Reviewer's Proposed Incidence				
BZA 20mg / CE 0.45mg	261	0	0.00	1.14
BZA 20mg / CE 0.625mg	(b) (4)			
MPA 1.5mg / CE 0.45mg	119	0	0.00	2.49
Placebo	135	0	0.00	2.19

UL 1-S = upper limit 1-sided
Source: Study Report 304; pages 56-58 of 1488

The incidence of endometrial hyperplasia through 24 months in Study 304 is shown in Table 94.

Table 94: Cumulative Incidence of Endometrial Hyperplasia at Month 24 in Study 304 – Efficacy Evaluable Population

Treatment Group	N	n	Incidence of Hyperplasia (%)	95% Confidence Interval UL 1-S
Applicant's Proposed Incidence				
BZA 20mg / CE 0.45mg	131	0	0.00	2.26
BZA 20mg / CE 0.625mg	(b) (4)			
MPA 1.5mg / CE 0.45mg	66	0	0.00	4.44
Placebo	79	0	0.00	3.72
Clinical Reviewers Proposed Incidence				
BZA 20mg / CE 0.45mg	131	0	0.00	2.26
BZA 20mg / CE 0.625mg	(b) (4)			
MPA 1.5mg / CE 0.45mg	66	0	0.00	4.44
Placebo	79	0	0.00	3.72

Note: The 7 subjects proposed by the Applicant include: 404885, 401263, 401338, 404490, 405065, 402641 and 403515. The clinical reviewer would also include 403068 and 401708
Source:

Reviewer's Comment:

(b) (4)

The Applicant was asked to provide a correlation between the 2 formulations used in Study 304 (formulation B and C) and the subjects who developed hyperplasia.

Endometrial Polyps in Study 304

The incidence of polyps identified in routine endometrial biopsies and confirmed by readings of at least 2 pathologists is summarized in Table 95. The table was modified by this reviewer to include information also from the 1 year extension.

Table 95: Incidence of Polyps in Scheduled Endometrial Biopsies at Screening, Month 12 and Month 24 (Polyps diagnosed by at least 2 pathologists)

Treatment Group	Time of Biopsy	N	n	Incidence	p-Value vs Placebo
BZA 20mg/CE 0.625mg	S	(b) (4)			
	Month 12				
	Month 24				
BZA 20mg/CE 0.45mg	S	361	8	2.22	1.000
	Month 12	266	5	1.88	0.172
	Month 24	133	3	1.69	0.295
MPA 1.5mg/CE 0.45mg	S	179	7	3.91	
	Month 12	122	3	2.46	
	Month 24	67	2	2.99	
Placebo	S	172	3	1.74	
	Month 12	136	0	0.00	
	Month 24	0	0	0.00	

Source: Study Report for 304; page 148 of 1488

Reviewer's Comment: There is only a limited amount of information to be gained from this table. Identification of polyps at screening did not exclude subjects from the trial. Endometrial biopsies are typically aspiration techniques with a catheter that may or may not remove a polyp. Polyps can also resolve on their own. Therefore the number of subjects with polyps at 12-24 months may reflect a polyp that is still present from the time of screening, a polyp that was undetected at screening or a new polyp. The key point is that incidence of polyps identified on treatment with study drug shows no signal of large increase over that at screening.

In regard to hysteroscopically identified endometrial polyps (confirmed by 2 pathologists) the subjects are shown in Table 96 for Study 304 including by dose group (Table 97).

Table 96: Polyps identified in Subject in Study 304 who Underwent Hysteroscopy

Subject Id	Age	Rx	Study Day	Pathologist + Histologic Findings
401909	53	BZA 20mg / CE 0.45mg	373	(b) (4) = endometrial polyp present endometrial polyp present = endometrial polyp present
400711	55	BZA 20mg / CE 0.45mg	118	endometrial polyp present endometrial polyp present
400827	50	BZA 20mg / CE 0.45mg	759	endometrial polyp present endometrial polyp present
(b) (4)		BZA 20mg / CE 0.625mg	(b) (4)	endometrial polyp present endometrial polyp present = endometrial polyp present
		BZA 20mg / CE 0.625mg		endometrial polyp not present endometrial polyp present = endometrial polyp present
		BZA 20mg / CE 0.625mg		endometrial polyp present endometrial polyp present
		BZA 20 mg / CE 0.625 mg		endometrial polyp present endometrial polyp present = endometrial polyp present
		BZA 20mg / CE 0.625mg		endometrial polyp present endometrial polyp present
		BZA 20mg / CE 0.625mg		endometrial polyp not present endometrial polyp present = endometrial polyp present
400867	52	MPA 1.5mg/ CE 0.45mg	372	endometrial polyp present endometrial polyp present
404056	58	MPA 1.5mg/ CE 0.45mg	376	endometrial polyp present endometrial polyp present = endometrial polyp not present

Source: Reviewer's analysis of Individual Efficacy and Response Data (16.2.6)

Table 97: Number of Subjects with Endometrial Polyp Identified by Hysteroscopy over 2 years in Study 304

Treatment group	Number of subjects
BZA 20mg/CE 0.625mg	(b) (4)
BZA 20mg/CE 0.45mg	3
MPA 1.5mg/CE 0.45mg	2
Placebo	0

Source: Source: Reviewer's analysis of Individual Efficacy and Response Data

6.4.3 Study 3307

Assessment for Endometrial Hyperplasia

The primary safety objective of Study 3307 was to confirm the endometrial safety of BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg based on an endometrial hyperplasia incidence of less than 1% at Year 1.

Reviewer's Comment: The endometrial hyperplasia assessment was identical to that of Study 304 which had 2 modifications (previously described) compared to Study 303. The only other difference was the fact that (b) (4) was the primary pathologist for Study 3307 and not (b) (4)

Endometrial Biopsy Results in Study 304

1. Disordered Endometrium in Study 3307

Disordered proliferative endometrium is characterized by an otherwise typical proliferative endometrium with very focal cystic change and minor glandular crowding. Although this category was not included officially in the category list for Study 3307 the pathologists in the comment section often added this term. In Table 98 below all the subjects who had at least one pathologist characterize their specimen as disordered are included.

Table 98: Disordered Endometrium in Study 3307

Subject Id	Age	Rx	Study Day	Pathologist + Histologic Findings
70070	52	BZA 20mg / CE 0.45mg	351	(b) (4) proliferative endometrium other (disordered endometrium)
708461	53	BZA 20mg / CE 0.45mg	209	endometrial tissue, other other (disordered endometrium)
(b) (4)		BZA 20mg / CE 0.625mg	(b) (4)	(b) (4) secretory endometrium (disordered) simple hyperplasia without atypia complex hyperplasia without atypia
		BZA 20mg / CE 0.625mg		endometrial tissue, other other (disordered endometrium)
		BZA 20mg / CE 0.625mg		proliferative endometrium other (disordered endometrium)
		BZA 20mg / CE 0.625mg		endometrial tissue, other other (disordered endometrium)
		BZA 20mg / CE 0.625mg		proliferative endometrium (disordered) endometrial tissue, other
		BZA 20mg / CE 0.625mg		proliferative endometrium (disordered) other (disordered endometrium)
		BZA 20mg / CE 0.625mg		proliferative endometrium (disordered) simple hyperplasia without atypia (single small focus) (b) (4) endometrial tissue, other
700870	61	MPA 1.5mg / CE 0.45mg	354	(b) (4) proliferative endometrium other (disordered endometrium)
702310	51	MPA 1.5mg / CE 0.45mg	350	weakly proliferative endometrium other (disordered endometrium)
702270	53	Placebo	365	(b) (4) simple hyperplasia without atypia other (disordered endometrium) weakly proliferative endometrium
705009	50	Placebo	392	proliferative endometrium other (weakly proliferative disordered endometrium)
706239	47	Placebo	352	(b) (4) proliferative endometrium other (disordered endometrium)

Source: Listing of endometrial biopsy results (comments section) in Study 3307

Reviewer's Comment:
The results are similar to Study 304 with the higher dose CE showing more cases of disordered proliferative endometrium.

2. Endometrial Hyperplasia Cases in Study 3307

All the subjects in Study 3307 with a diagnosis of endometrial hyperplasia by at least one pathologist are shown in Table 99.

Table 99: Endometrial Hyperplasia in Study 3307

Subject Id	Age	Rx	Study Day	Pathologist + Histologic Findings
701129	52	BZA 20mg / CE 0.45mg	357	(b) (4) endometrial tissue,other (minimal gland crowding) (b) (4) simple hyperplasia without atypia (b) (4) complex hyperplasia with atypia
(b) (4)		BZA 20mg / CE 0.625mg	(b) (4)	(b) (4) secretory endometrium (disordered) simple hyperplasia without atypia complex hyperplasia without atypia
		BZA 20mg / CE 0.625mg		simple hyperplasia without atypia endometrial tissue, other weakly proliferative endometrium
		BZA 20mg / CE 0.625mg		proliferative endometrium (disordered) simple hyperplasia without atypia (single small focus) (b) (4) endometrial tissue, other
702270	53	Placebo	365	(b) (4) simple hyperplasia without atypia other (disordered endometrium) weakly proliferative endometrium
708222	56	Placebo	363	complex hyperplasia without atypia (small fragments) (b) (4) endometrial tissue, other weakly proliferative endometrium
712593	49	Placebo	355	complex hyperplasia with atypia simple hyperplasia without atypia

Source: Individual efficacy and response data and diopee dataset

Reviewer's Comment: Based on the pathology diagnoses in the prior table this reviewer considers that each of the BZA/CE treatment groups had 1 case of endometrial hyperplasia along with 1 case in the placebo group.

3. Endometrial Hyperplasia Incidence in Study 3307

The incidence of endometrial hyperplasia through 12 months in Study 3307 is shown in Table 100.

Table 100: Incidence of Endometrial Hyperplasia at Month 12 in Study 3307 (Efficacy Evaluable Population)

Treatment Group (a)	N	n	Incidence of Hyperplasia (%)	Upper Limit 95% CI (1-sided)
BZA 20mg / CE 0.45mg	335	1	0.30	1.41
BZA 20mg / CE 0.625mg	(b) (4)			
BZA 20mg	169	0	0.00	1.76
MPA 1.5mg / CE 0.45mg	149	0	0.00	1.99
Placebo	354	1	0.28	1.33

BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; CI= confidence interval
Source: Study Report 3307 page 95 of 2153 (Table 9-1)

Reviewer's Comment: This reviewer finds that the endometrial hyperplasia rate for the proposed to-be-marketed doses of BZA/CE are acceptable in Study 3307.

Endometrial Polyps in Study 3307

The incidence of polyps in scheduled endometrial biopsies are shown in Table 101.

Table 101: Incidence of Polyps in Scheduled Endometrial Biopsies at Screening and Month 12 (Polyps diagnosed by at least 2 pathologists)

Treatment	Time of Biopsy	N	n	Incidence	p-Value vs Placebo
BZA 20mg/CE 0.625mg	S	(b) (4)			
	Month 12				
BZA 20mg/CE 0.45mg	S	445	5	1.12	0.580
	Month 12	338	7	2.07	0.033
BAZ 20mg	S	230	4	1.74	1.000
	Month 12	171	1	0.58	0.544
MPA 1.5mg/CE 0.45mg	S	220	7	3.18	0.261
	Month 12	153	4	2.61	0.030
Placebo	S	474	8	1.69	
	Month 12	356	1	0.28	

Source: Study Report for 304; page 148 of 1488

Reviewer's Comment: Similar to study 304 there is only a limited amount of information to be gained from this table. Identification of polyps at screening did not exclude subjects from the trial. Endometrial biopsies are typically aspiration techniques with a catheter that may or may not remove a polyp. Polyps can also resolve on their own. Therefore the number of subjects with polyps at 12 months may reflect a polyp that is still present from the time of screening, an undetected polyp or a new polyp. The key point is that incidence of polyps identified on treatment with study drug shows no signal of large increase over that at screening.

Endometrial polyps diagnosed after hysteroscopy are shown in Table 102 for Study 3307 (polyps were identified by at least 2 pathologists) and by dose group (Table 103).

Table 102: Polyps Identified in Study 3307 after Hysteroscopy (Confirmed by 2 Pathologists)

Subject Id	Age	Rx	Study Day	Pathologist + Histologic Findings
(b) (4)		BZA 20mg / CE 0.625mg	(b) (4)	(b) (4) endometrial polyp present endometrial polyp not present endometrial polyp present
		BZA 20mg / CE 0.625mg		endometrial polyp present endometrial polyp not present endometrial polyp present
		BZA 20mg / CE 0.625mg		endometrial polyp present endometrial polyp present
700365	56	MPA 1.5mg/ CE 0.45mg	371	endometrial polyp present endometrial polyp not present endometrial polyp present
706219	51	MPA 1.5mg/ CE 0.45mg	377	endometrial polyp present endometrial polyp present
706861	55	BZA 20mg	419	endometrial polyp present endometrial polyp present

Table 103: Number of Subjects with Endometrial Polyp Identified by Hysteroscopy over 1 year in Study 3307 by at Least 2 Pathologists

Treatment group	Number of subjects
BZA 20mg/CE 0.625mg	(b) (4)
BZA 20mg/CE 0.45mg	0
BZA 20mg	1
MPA 1.5mg/CE 0.45mg	2
Placebo	0

Source: 3307 Study Report; page 266 of 2153

6.4.3 Combined Study Information for Endometrial Protection

The Applicant provided data from Studies 303 and 3307 to support the endometrial protective properties of BZA when used in conjunction with CE.
Study 304 was only considered by the Applicant as providing supportive evidence for endometrial protection because the BZA component of 1 of the formulations used (formulation C) was approximately 18% lower in bioavailability compared to the formulation used in Study 303 (formulation A).

Table 104 combines the endometrial hyperplasia/malignancy incidence data for BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg through 12 months of use in Studies 303, 304 and 3307 (based on the analysis of this reviewer).

Table 104: Endometrial Hyperplasia/Malignancy Rate for BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg in Studies 303, 304 and 3307 Through 12 Months of Use

Study	Treatment	N	n	Hyperplasia rate (%)	1-S 95% CI UL
303	BZA 20mg/CE 0.45mg	335	0	0.00	0.89
	BZA 20mg/CE 0.625mg	(b) (4)			
304	BZA 20mg/CE 0.45mg	261	0	0.00	1.14
	BZA 20mg/CE 0.625mg	(b) (4)			
3307	BZA 20mg/CE 0.45mg	335	1	0.30	1.41
	BZA 20mg/CE 0.625mg	(b) (4)			

N = number of subjects; n = number of subjects with hyperplasia/malignancy; 1-S 95% CI UL = one-sided 95% confidence interval upper limit

Table 105 combines the endometrial hyperplasia/malignancy incidence data for BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg through 24 months of use in Studies 303 and 304 (based on the analysis of this reviewer).

Table 105: Endometrial Hyperplasia/Malignancy Rate for BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg in Studies 303 and 304 Through 24 Months of Use.

Study	Treatment	N	n	Hyperplasia rate (%)	1-S 95% CI UL
303	BZA 20mg/CE 0.45mg	293	2	0.68	
	BZA 20mg/CE 0.625mg	(b) (4)			
304	BZA 20mg/CE 0.45mg	131	0	0.00	2.26
	BZA 20mg/CE 0.625mg	(b) (4)			

Reviewer's Comment: There is no evidence of concern in regard to endometrial hyperplasia for the BZA 20mg/CE 0.45mg dose through either 12 or 24 months of use. (b) (4) **This reviewer also concurs that** (b) (4) **the lower dose should be the only one that is carried forward to approval.**

6.4.4 Combined Study Information for Endometrial Polyps

In the Clinical Summary of Safety the Applicant had the following conclusions about endometrial polyps:

- BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were associated with slightly higher incidence of endometrial polyps as compared to placebo. Endometrial polyps identified during the conduct of the BZA/CE Phase 3 studies were benign and asymptomatic. The incidence of endometrial polyps in the BZA 20 mg/CE dose groups is comparable to the incidence observed in the CE/MPA treatment group and historical data.

Reviewer's Comment:
Although this reviewer does not have any disagreements with the conclusions or sees any clinically significant safety signal regarding polyps there are a number of difficulties with analyzing polyps that should be mentioned:

Endometrial biopsies are typically catheter aspiration procedures which will only retrieve very small polyps or fragments of polyps. There may also be many cases in which a catheter pulls in endometrial tissue from around a polyp and leaves the polyp behind.

Diagnosis of a polyp fragment under the microscope can be very subjective and often based on subtle changes in the endometrial stroma and glands.

Since subjects were not excluded for endometrial polyps it is possible that polyps diagnosed at 12 and 24 months could be residual polyp tissue left over from the time of screening, polyps that were present at screening and undetected or new ones that have developed during the study. This makes the analysis of polyps in the routinely collected endometrial biopsy material very difficult to interpret.

The use of transvaginal sonography at the time of screening to excluded subjects with endometrial stripes > 4mm or with focal abnormalities is also not a perfect imaging system. A number of subjects were found at the time of screening with different types of endometrial polyps (endometrial biopsies read by the central pathologists) that either fit within the 4mm measurement or were not identified by sonography.

Hysteroscopy may be more accurate in that polyps can be directly visualized and biopsied. However the number of hysteroscopic procedures was small compared to the scheduled endometrial biopsies performed. Hysteroscopy in these studies could have been slightly skewed towards those subject taking hormones because a decision for hysteroscopy was based on specific transvaginal findings (endometrial thickness greater than 8mm or a focal abnormality). In other words there could be some placebo subjects with endometrial polyps < 8mm with no significant imaging abnormality who are not represented in the table below. Hysteroscopically detected polyps from Studies 303, 304 and 3307 are listed in Table 106.

Despite the previous caveats about the reliability of polyp diagnosis this reviewer feels that the hysteroscopic results below could justify the Applicant's statement from above about a "slightly higher" incidence of polyps in the BZA/CE treatment arms compared to placebo. This reviewer also believes that a statement in the label could also suggest this relationship. Albeit the numbers were small but Study 303 suggests some dose response in regard to polyps. This reviewer does not feel that polyp safety data impacts the approvability of the product.

Table 106: Endometrial Polyps Identified through Hysteroscopy in Studies 303, 304 and 3307

Treatment	Study 303	Study 304	Study 3307	Total
BZA 10mg/CE 0.45mg	1	---	---	1
BZA 20mg/CE 0.45mg	2	3	0	5
BZA 40mg/CE 0.45mg	0	---	---	0
BZA 10mg/CE 0.625mg	(b) (4)			
BZA 20mg/CE 0.625mg				
BZA 40mg/CE 0.625mg	2	---	---	2
BZA 20mg	---	---	1	1
Raloxifene 60mg	0	---	---	0
MPA 1.5mg/CE 0.45mg	---	2	2	4
Placebo	0	0	0	0

7 Review of Safety

Safety Summary

Both doses of conjugated estrogen/bazedoxifene intended for registration, the CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg doses, with the exception of endometrial hyperplasia in study 304, were well tolerated in the one Phase 2 and 5 Phase 3 trials. All trials included a placebo control group. The Phase 2 trial compared CE 0.3 and 0.625 mg combined with (as separate tablets) BZA 5, 10, and 20 mg with active comparators CE 0.3 and 0.625 mg alone, BZA 5 mg alone, and CE 0.625/medroxyprogesterone 2.5 mg. The Phase 3 Trial 303 included CE 0.45/BZA 10, CE 0.45/BZA 40, CE 0.625/BZA 10, and CE 0.625/BZA 40 groups. Various Phase 3 trials included BZA 20 mg, raloxifene 60 mg, and/or CE 0.45/MPA 1.5 as active comparators.

The risk of VTE associated with BZA is well-documented. The BZA monotherapy program for prevention and treatment of postmenopausal osteoporosis received complete response letters due to excess VTE and potential CVA risks (b) (4) . The rate of VTE, defined as DVT, PE, and retinal vein thrombosis, in Study 301, a three year fracture study in osteoporotic postmenopausal women and the largest of the BZA monotherapy trials, was 35 per 10,000 woman-years for BZA 20 mg daily

and 34 per 10,000 woman years for BZA 40 mg daily, compared to 22 per 10,000 woman years for raloxifene and 17 per 10,000 woman years for placebo. The risk of VTE per 10,000 women-years in the WHI estrogen alone substudy was 28 for CE 0.625 mg compared to 21 for placebo. The rate of stroke in Study 301 was 37 per 10,000 woman-years for BZA 20 mg daily and 47 per 10,000 woman years for BZA 40 mg daily, compared to 20 per 10,000 woman years for raloxifene and 30 per 10,000 woman years for placebo. In the WHI estrogen alone substudy, the all stroke rate on CEs was 45 per 10,000 woman years compared to 33 for placebo. For the estrogen plus progestin substudy, rates were 33 and 25 respectively.

Unexpectedly, VTE rates in Trial 303 in this NDA were 7 per 10,000 woman years in all CE/BZA treatment groups combined. Two of the three events occurred in the CE 0.625 mg/BZA 40 mg treatment group. No VTEs were reported in the raloxifene group and only one was reported in placebo (14 per 10,000 woman years). Stroke rates in Trial 303 were 7 per 10,000 woman years in all CE/BZA treatment groups combined, with no more than one stroke event per group. No strokes were reported in the raloxifene group or placebo (about 700 woman years of exposure each). In Trial 3307, one case of VTE was reported in the CE/MPA group only, and one stroke case in the CE 0.625 mg/BZA 20 mg treatment group (rate 24 per 10,000 woman years but difficult to assess true frequency with a single case, no cases in the CE 0.45/BZA 20 mg group). No cases of VTE or stroke were reported with bazedoxifene monotherapy or placebo. In Trial 304, VTE was reported only in 3 subjects in the CE 0.45/BZA 20 mg group (66 per 10,000 woman years), with none in the CE 0.625 mg/BZA 20 mg, CE/MPA, or placebo groups. No cases of stroke were reported. No VTEs or stroke were reported in Trials 305 and 306.

The decreased rates of VTE and stroke seen in the CE/BZA program cannot be explained but underreporting of events across all dose groups may play a role. Lower than expected rates are also reported for CE/MPA, BZA monotherapy, raloxifene, and placebo treatment groups in CE/BZA trials. In addition, the interaction between BZA and CE is unknown. Based on what is known, these results/findings do not negate the risk of VTE/CVA following the administration of BZA/CE and warnings for similar products should be applied.

Coagulation parameters were followed in a subset of subjects in Trial 303, with smaller panels of coagulation laboratories followed in Trials 3307 and 204. Generally, there were not significant changes associated with BZA/CE administration on PT, PTT, protein C, plasminogen activator inhibitor-1 antigen, and D-dimer. Remaining factors affecting fibrinolysis (i.e. plasminogen activity, plasminogen activator inhibitor 1activity) changed in a way which would enhance clot resolution. Fibrinogen, a procoagulant factor, was decreased in all BZA/CE treatment groups. The small differences in antithrombin III and Protein S between the BZA/CE groups and placebo were unlikely to be clinically meaningful.

Deaths were infrequent, with no deaths noted in Phase 1 or 2. In Phase 3, no deaths occurred on CE 0.45/BZA 20, 2 deaths (0.1%) on CE 0.625/BZA 20, and 3 deaths (0.2%) on placebo. No concerning pattern was noted.

Serious adverse events occurred in similar percentages of subjects across treatment groups (4% CE 0.45/BZA 20, 4% CE 0.625/BZA 20, 5% placebo). SAEs were present in small numbers and were balanced between treatment groups.

Adverse events leading to withdrawal occurred in similar percentages of subjects across treatment groups (8% CE 0.45/BZA 20, 8% CE 0.625/BZA 20, 10% placebo). Adverse events leading to withdrawal were present in small numbers and were generally balanced between treatment groups. For the placebo group in Trial 303, an increase in withdrawals for osteoporosis (6 subjects, 1%, no more than 2 in any other group) likely due to the natural history of bone loss in menopause. (b) (4)

In the WHI estrogen plus progestin substudy, there was an increased risk of coronary artery disease events compared to placebo. No overall difference was seen the in the WHI estrogen-only substudy. No overall difference in cardiovascular events was seen in the bazedoxifene monotherapy trial 301 nor in the CE/BZA combination trials.

No excess of breast cancer, uterine cancer, or ovarian cancer events was reported with CE/BZA. Relatively few cases of breast cancer and very few of uterine and ovarian cancer were reported.

Breast adverse events appeared generally balanced between treatment groups. Breast pain or tenderness was the most common adverse event.

Uterine adverse events were concentrated in the CE/BZA 10 groups of Trial 303 and included vaginal hemorrhage, endometrial hyperplasia, vaginal discharge, genital discharge, and ultrasound uterus abnormal. Uterine polyps were more common in Trial 303 in all conjugated estrogen treatment groups except the BZA 40 mg/CE 0.45 mg group. (b) (4)

Fractures were collected as adverse events. Fractures were generally balanced between groups.

To evaluate common adverse events, on- and post-treatment adverse events were combined for Trials 303 and 3307. In general, adverse events were similar between treatment groups. At least one adverse event was reported by 90 to 92% of subjects in

the CE 0.45/BZA 20, CE 0.625/BZA 20, or placebo groups. The SOCs with the largest number of events were Infections and Infestations (overall 54% of subjects reporting), Musculoskeletal and Connective Tissue Disorders (51%), Gastrointestinal Disorders (39%), and Nervous System Disorders (39%). The most common preferred terms were headache (overall 30% of subjects reporting), back pain (20%), arthralgia (20%), nasopharyngitis (16%), pain in extremity (13%), influenza (13%), and myalgia (11%).

A trend of more GI SOC adverse events with CE/BZA is noted (44% of subjects with CE 0.45/BZA 20, 38% CE 0.625/BZA 20, 36% placebo). The preferred terms that seem to account for this increase are abdominal pain, abdominal pain upper, diarrhea, and nausea.

A trend of more Respiratory SOC adverse events with CE/BZA is noted (23% of subjects with CE 0.45/BZA 20, 20% CE 0.625/BZA 20, 18% placebo). Increases in several preferred terms seem to account for this (oropharyngeal pain, nasal congestion, rhinitis seasonal, sinus congestion, upper respiratory tract congestion).

A trend of more Skin and Subcutaneous Tissue SOC adverse events with CE/BZA is noted (18% of subjects with CE 0.45/BZA 20, 18% CE 0.625/BZA 20, 15% placebo). Increased alopecia (3% of subjects with CE 0.45/BZA 20, 3% CE 0.625/BZA 20, 1% placebo) and dry skin (2% of subjects with CE 0.45/BZA 20, 2% CE 0.625/BZA 20, 1% placebo) with CE/BZA seem to be primarily responsible. Urticaria was reported by 11 subjects (1%) with CE 0.45/BZA 20, 8 subjects (1%) with CE 0.625/BZA 20, and 3 subjects (<1%) with placebo.

The Reproductive System and Breast Disorder SOC showed similar percentages of subjects with AEs between groups (24% of subjects with CE 0.45/BZA 20, 23% CE 0.625/BZA 20, 23% placebo).

The preferred term nasopharyngitis was more frequently reported in the CE/BZA arms (19% of subjects with CE 0.45/BZA 20, 16% CE 0.625/BZA 20, 14% placebo). The preferred term muscle spasm was more frequently reported in the CE/BZA arms (11% of subjects with CE 0.45/BZA 20, 8% CE 0.625/BZA 20, 6% placebo). Hot flushes were reported in similar percentages of subjects (5% of subjects with CE 0.45/BZA 20, 6% CE 0.625/BZA 20, 7% placebo). Triglycerides increased (4% of subjects with CE 0.45/BZA 20, 3% CE 0.625/BZA 20, 2% placebo) and hypertriglyceridemia (4% of subjects with CE 0.45/BZA 20, 4% CE 0.625/BZA 20, 3% placebo) were also reported in similar percentages of subjects.

The most consistent laboratory findings in the Phase 3 trials were an increase in triglycerides with CE/BZA. Where evaluated, it would appear the mean increase was about 5 to 20%. Alkaline phosphatase was overall mildly decreased, probably due to bone antiresorptive effect. Transaminases and bilirubin were not increased. Creatinine

and BUN were not significantly change. Slight reductions of serum calcium and phosphate were noted with CE/BZA.

No clear increases in blood pressure or weight were noted in Phase 3 trials with CE/BZA.

No clear excess of concerning ECG events was found with CE/BZA. A definitive QT study for bazedoxifene was negative (b) (4) and a QT study using CE/BZA was not required.

(b) (4)

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Phase 3 trials analyzed for safety are shown in Table 107. Treatment groups representing conjugated estrogen/bazedoxifene at doses considered for registration, along with active comparators and placebo, are shaded. All of these trials were done in healthy postmenopausal women age 40 to 65, except as noted, with intact uteri and acceptable endometrial biopsy results at screening (evaluable tissue, no hyperplasia). Trials were double-blind, randomized, and placebo controlled, with some trials having active control groups as well.

The primary source used for safety data is Trial 303, as this was the longest of the large trials with a duration of 2 years. Treatment arms with bazedoxifene doses not considered for registration (10 and 40 mg in combination with CE) will only peripherally be considered in this review. The primary objective of this trial was to evaluate the effect of CE/BZA on the incidence of endometrial hyperplasia in postmenopausal women after 1 year of therapy. Two osteoporosis prevention substudies were included. Age range at screening was 40 to 75.

Trial 3307 was a one year confirmatory trial to evaluate the effect of CE/BZA on the incidence of endometrial hyperplasia in postmenopausal women. An osteoporosis substudy measured efficacy in preventing postmenopausal osteoporosis. Sleep and breast density substudies were also performed. Although shorter than Trial 303, data from this trial will often be combined with that from Trial 303 for analysis.

The primary objective of Trial 304 was to evaluate the effect of CE/BZA on the incidence of endometrial hyperplasia in postmenopausal women after 1 year of therapy. An osteoporosis substudy measured efficacy in preventing postmenopausal

osteoporosis. Subjects in Trial 304 were started on Formulation B. After 3 to 9 months, subjects were transitioned to Formulation C. (b) (4) A year-long extension was initiated to provide further efficacy and safety data for the Formulation C. All subjects took formulation C the second (extension) year of the trial. Safety results from Trial 304 must be considered (b) (4)

Trials 305 and 306 were smaller (around half or fewer the subjects per CE/BZA treatment arm) and shorter (12 weeks) compared to the other trials considered here. Trial 305 assessed treatment of moderate to severe vasomotor symptoms. Trial 306 assessed treatment of vulvovaginal atrophy.

Table 107: Phase 3 Trials in NDA 22247 Analyzed for Safety

Study number/ Population[1]	Usual reference	Primary objective	Duration	Treatment groups	N
3115A1-303/ to age 75, two OP prevention substudies with additional criteria	303	Endometrial hyperplasia after 1 year	2 years	CE 0.45 mg/BZA 10 mg	430
				CE 0.45 mg/BZA 20 mg	433
				CE 0.45 mg/BZA 40 mg	423
				CE 0.625 mg/BZA 10 mg	430
				CE 0.625 mg/BZA 20 mg	414
				CE 0.625 mg/BZA 40 mg	417
				Raloxifene 60 mg	423
				Placebo	427
3115A1-304/ BMD substudy < 5 years PM, T-score ≥ -2.5	304	Endometrial hyperplasia, preventing PMO after 1 year	1 year	CE 0.45 mg/BZA 20 mg	361
				CE 0.625 mg/BZA 20 mg	349
				CE 0.45 mg/MPA 1.5 mg	179
				Placebo	172
3115A1-304 (extension)	304	Additional efficacy and safety data (formulation with lower BZA bioavailability)	1 year extension	CE 0.45 mg/BZA 20 mg	168
				CE 0.625 mg/BZA 20 mg	177
				CE 0.45 mg/MPA 1.5 mg	84
				Placebo	94
3115A1-305/ Hot flashes	305	Treatment of VMS	12 weeks	CE 0.45 mg/BZA 20 mg	127
				CE 0.625 mg/BZA 20 mg	128
				Placebo	63
3115A1-306/ VVA symptoms	306	Treatment of VVA	12 weeks	CE 0.45 mg/BZA 20 mg	219
				CE 0.625 mg/BZA 20 mg	218
				BZA 20 mg	110
				Placebo	105
3115A1-3307/ Substudies BMD, sleep, breast density with additional criteria	3307	Endometrial hyperplasia, preventing PMO after 1 year	1 year	CE 0.45 mg/BZA 20 mg	445
				CE 0.625 mg/BZA 20 mg	474
				BZA 20 mg	230
				CE 0.45 mg/MPA 1.5 mg	220
				Placebo	474

Source: NDA 22247, 5.3.5.3, Integrated Summary of Safety, Table 0-1
1 All of these trials were done in healthy postmenopausal women age 40 to 65, except as noted, with intact uteri and acceptable endometrial biopsy results at screening. Additional major population criteria, if any, are listed

A total of 6041 postmenopausal women received various combinations of BZA (5, 10, 20, and 40 mg) and CE (0.3, 0.45, and 0.625 mg) as a single oral dose or daily oral doses for up to 24 months. Phase 1 studies evaluated BZA 10 to 40 mg with CE 0.625 mg as single doses or daily doses up to 14 days. The single Phase 2 study (Trial 203) evaluated BZA 5 mg, 10 mg, and 20 mg co-administered with CE 0.3 mg and 0.625 mg for 3 months as separate tablets. The subjects in the Phase 3 studies (Trials 303, 304, 305, 306, and 3307) received BZA at doses of 10, 20, and 40 mg in combination with CE 0.45 mg or 0.625 mg as a single tablet for up to 2 years.

Duration of exposure for Phase 3 subjects is shown in Table 108, although only CE/BZA doses intended for registration are listed. For CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg 1089 and 1097 subjects have been treated for at least 6 months

respectively and 987 and 1006 for a year. Thus, this application exceeds ICH-E1A recommendations of at least 1500 subjects exposed, with 300-600 exposed for at least 6 months and 100 for a year for drugs intended for long-term treatment of non-life-threatening conditions.

Table 108: Duration of Treatment for Subjects in Phase 3 Trials of CE/BZA

Treatment interval	CE 0.45/ BZA 20	CE 0.625/ BZA 20	CE 0.45/ MPA 1.5	BZA 20	Raloxifene	Placebo
Taken at least to	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Week 1	1585 (100)	1583 (100)	399 (100)	340 (100)	423 (100)	1241 (100)
Week 12	1468 (93)	1466 (93)	355 (89)	313 (92)	390 (92)	1156 (93)
Week 25	1089 (69)	1097 (69)	326 (82)	197 (58)	353 (83)	934 (75)
Week 49	987 (62)	1006 (64)	291 (73)	187 (55)	310 (73)	849 (68)
Week 101	440 (28)	428 (27)	68 (17)	0	269 (64)	360 (29)
Source: NDA022247, GSR 0000, 5.3.5.3 (Integrated Summary of Safety) Table 1-8						

7.1.2 Categorization of Adverse Events

Upon NDA submission, it was noted that multiple versions of MedDRA (and COSTART) being used to code adverse events in clinical studies in this application. An information request was sent November 6, 2012, asking the Applicant to recode the adverse events using the most recent version of MedDRA. On November 30, a submission was received which contained tables and datasets for the Phase 3 CE/BZA trails and integrated summary of safety recoded to MedDRA version 15.1.

Datasets were reviewed from Trials 303 and 3307 comparing the verbatim term with the coded preferred term for withdrawals, possible variants of DVT, and a sample of the overall dataset. In general, the coding appeared appropriate with no major discrepancies noted.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Populations for all of the Phase 3 trials are reasonably similar (healthy postmenopausal women age 40 to 65, except to age 75 in Trial 303, with intact uteri and acceptable endometrial biopsy results at screening). For overall adverse events, Trials 303 and 3307 will be combined for analysis. Trial 304 will be excluded due to the use of a formulation, Formulation C, (b) (4) and Trials 305 and 306 will be excluded due to short duration (3 months compared to 12 to 24 months for other trials) and small size (half or less the CE/BZA treatment group size). The trials excluded from the overall evaluation will be included or discussed where appropriate in evaluation of specific safety concerns.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As noted in 7.1.1 above, this application exceeds ICH-E1A recommendations of at least 1500 subjects exposed, with 300-600 exposed for at least 6 months and 100 for a year for drugs intended for long-term treatment of non-life-threatening conditions. Enough subjects are included to adequately evaluate the risk of venous thromboembolism and stroke as discussed in 7.3.5 below. Sufficient subjects were exposed for a sufficient duration to evaluate uterine safety.

Phase 3 trials were double-blind, randomized, and placebo controlled, with some trials having active control groups as well. The population studied was healthy postmenopausal women with a mean age of 55 years and an age range of 40 to 75 years and mean body mass index of 26 kg/m^2. The majority of subjects enrolled in the trials were less than age 65 years. A total of 77 of 3168 subjects (2.4%) in CE/BZA 20 mg treatment groups in Phase 3 studies were age 65 to 75. This drug product has not been studied in women over age 75 years. The mean time since menopause was 6 – 7 years. All enrolled subjects had an intact uterus and acceptable endometrial biopsy results at screening. This corresponds well to the population expected to take an estrogen-based drug with uterine protection for prevention of osteoporosis and treatment of vasomotor symptoms and vulvovaginal atrophy.

7.2.2 Explorations for Dose Response

Trial 203 evaluated CE at 0.3 or 0.625 mg in combination with BZA at 5, 10, and 20 mg in a Phase 2 dose-finding study of 12 weeks duration. The BZA 20 mg dose was the lowest dose that provided sufficient endometrial protection. For VMS, the Phase 2 study showed that CE 0.3 was insufficient to provide enough vasomotor or vulvar vaginal atrophy efficacy in combination with BZA 20 mg.

Trial 303 evaluated conjugated estrogen at either 0.45 or 0.625 mg in combination with bazedoxifene at 10, 20, and 40 mg for two years. BZA 20 and 40 mg with either CE 0.45 mg or 0.625 mg doses were well tolerated in this two year trial in postmenopausal women. The CE 0.45 mg/BZA 10 mg and CE 0.625 mg/ BZA 10 mg doses were not well tolerated due to endometrial and uterine safety issues. See uterine safety review in Section 6.4. The CE 0.45 mg/BZA 20 mg and CE 0.625 mg/ BZA 20 mg doses are the doses for which registration is being sought.

7.2.3 Special Animal and/or In Vitro Testing

A mouse model of thrombosis (time to occlusion of the femoral vein with 15% $FeCl_3$ applied to the surgically exposed adventitial surface) demonstrated BZA alone did not affect the mean time to occlusion. CE and CE + MPA did numerically reduce the time to occlusion, but only slightly, and was only statistically significant for the combination of CE + MPA. This result is counter to what was observed in the bazedoxifene monotherapy trials, where venous thromboembolic events occurred more frequently with bazedoxifene when compared to placebo. BZA appeared to prevent the CE-induced reduction in time to occlusion, but since the CE effect was itself very small, it is difficult to interpret this finding. Further details will be found in the Pharmacology Toxicology review.

7.2.4 Routine Clinical Testing

In two year Trial 303, the following routine clinical testing was performed:

- Physical exam at Screening and every 6 months on study
- Height at Screening and yearly
- Blood pressure and weight at Screening, Baseline, and every 3 months
- Electrocardiogram at Screening and End of Study
- Laboratory safety determinations (hematology [hemoglobin, hematocrit, white blood cell count {differential only if abnormal}, platelets], fasting chemistry [sodium, potassium, chloride, glucose, BUN, creatinine, calcium, phosphorus, uric acid, total protein, albumin, cholesterol, triglycerides, total bilirubin, AST, ALT, alkaline phosphatase; free T4 and TSH only for subjects taking thyroid replacement therapy], urinalysis [pH, protein, ketones, blood]) at Screening, Months 3 and 6, then every 6 months. Chemistry only done at Month 9. HDL and LDL cholesterol measures were added to chemistry at Screening and Months 12 and 24.
- Gynecologic exam with cervical cytologic and vaginal smears at Screening and every 6 months
- Mammography at Screening and yearly
- Transvaginal ultrasound (TVU) at Screening and yearly in about a third of subjects. At sites performing TVUs, if the ultrasound at Month 12 or 24 identified non-measurable endometrium, double-wall thickness greater than 8 mm, or a focal abnormality, hysteroscopy with directed biopsy was performed in place of the routine biopsy.
- Endometrial biopsy at Screening and Months 6, 12, and 24
- FSH and serum 17 beta-estradiol at Screening
- Adverse event reporting was done at Screening, Baseline, and at every visit (every 3 months)
- Coagulation parameters prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III activity, protein C activity, protein S activity, plasminogen activity,

plasminogen activator inhibitor-1 activity, plasminogen activator inhibitor-1 antigen, and D-dimer were checked at Screening, Baseline, and every 6 months as part of the Osteoporosis Prevention II and Metabolic Substudy, about 25% of the population
- Lipid parameters including cholesterol, HDL, LDL, and VLDL cholesterol, triglycerides, VLDL triglycerides, HDL_2 and HDL_3 cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein (a) were checked at Screening, Baseline, and every 6 months in the Osteoporosis Prevention II and Metabolic Substudy
- Plasma homocysteine, TSH, C-reactive protein, and carbohydrates (fasting insulin and glucose) were checked at Baseline and every 6 months in the Osteoporosis Prevention II and Metabolic Substudy

In one year Trial 3307 the following routine clinical testing was performed:
- Physical exam at Screening and every 6 months on study
- Vital signs at Screening, Baseline, and every 6 months. BP at all, weight at all except Baseline, height only at Screening
- Electrocardiogram at Screening and End of Study
- Laboratory screen (hematology [red blood cell count, hemoglobin, hematocrit, white blood cell count {differential only if abnormal}, platelets], fasting chemistry [sodium, potassium, chloride, glucose, BUN, creatinine, calcium, phosphorus, uric acid, total protein, albumin, cholesterol {including HDL, LDL, and VLDL cholesterol}, triglycerides, total bilirubin {direct if abnormal}, AST, ALT, GGT, alkaline phosphatase], urinalysis [pH, protein, ketones, blood]) at Screening and Months 3, 6, and 12
- Sex hormone-binding globulin at Screening and Months 6 and 12
- FSH at Screening if LMP 6 to 12 months in the past
- Pelvic exam and PAP smear at Screening and End of Study
- TVU and endometrial biopsy at Screening and End of Study. If the ultrasound at Month 12 identified double-wall endometrial thickness greater than 8 mm or a focal abnormality, hysteroscopy with directed biopsy was performed in place of the routine biopsy
- Mammography at Screening and End of Study
- Adverse events were checked at all visits
- iPTH and 25-OH vitamin D at Screening for the Osteoporosis Substudy (about one third of the trial population)
- Coagulation parameters prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III activity, protein C activity, protein S activity, plasminogen activity, plasminogen activator inhibitor-1 activity, plasminogen activator inhibitor-1 antigen, and D-dimer at Screening and Months 6 and 12 for the Osteoporosis Substudy. Factor V Leiden was also checked at Screening

Central laboratories were used for both trials. Cytological smears and endometrial biopsies were centrally evaluated. Transvaginal ultrasounds were performed at the sites

by qualified TVU technologists in accordance with standardized study-specific procedures. The TVU scans were read locally by board-certified/board-eligible gynecologists or radiologists. A central service verified the proper calibration and maintenance of the TVU equipment. Electrocardiograms and mammograms were read locally at the study sites for both trials.

Routine clinical testing appears adequate both in type and frequency for Trials 303 and 3307.

7.2.5 Metabolic, Clearance, and Interaction Workup

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

No pharmacokinetic studies conducted in special populations are reported in the label for conjugated estrogen, including in patients with renal or hepatic impairment.

Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic dispositions of both drugs are not altered when the drugs are co-administered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects.

Bazedoxifene is metabolized primarily by glucuronidation with excretion of glucuronides almost entirely in the bile and elimination in the feces (Study 103). Bazedoxifene undergoes little or no cytochrome P450-mediated metabolism and reportedly does not

induce or inhibit the activities of major CYP isoenzymes. Given the mechanism of metabolism and excretion for bazedoxifene, renal impairment is not expected to affect pharmacokinetics. However, data from severe renally impaired postmenopausal patients (n=2) showed a 69% increase in BZA AUC following BZA 20 mg (Study 121). Due to the low number of subjects, it is not possible to conclude that renal impairment affects BZA exposure. There is a theoretical risk that renal impairment would decrease renal clearance of BZA/CE and increase the VTE risk. The sponsor has proposed not to recommend use in patients with renal impairment. Subjects with impaired hepatic function showed a 4-fold increase in bazedoxifene exposure (Study 112). The Applicant does not recommend use in patients with impaired hepatic function and this is acceptable per the clinical pharmacology team.

Data from single-dose drug-drug interaction studies involving conjugated estrogens and bazedoxifene indicate that the pharmacokinetic dispositions of both drugs are not altered when the drugs are co-administered. No drug interaction studies were conducted with CE/BZA.

See the Clinical Pharmacology review for further details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bazedoxifene: Bazedoxifene is an estrogen agonist/antagonist that is not approved as monotherapy. Complete Response letters were issued (b) (4) Possible increased risk of concerning adverse events included:

- Venous thromboembolism (VTE)
- Superficial thrombophlebitis, thrombophlebitis, phlebitis, and thrombosis
- Stroke
- TIA

In both Trials 303 and 3307 these were collected as adverse events and evaluated as adverse events of special interest, although in Trial 3307 these terms “trigger(ed) further evaluation to confirm final diagnosis”. There is no discussion of what occurred to further evaluate these terms in the study report or protocol. Based on the study report, no adjudication committee was convened to evaluate these events.

Raloxifene: Raloxifene is an estrogen agonist/antagonist, similar in chemical structure to bazedoxifene, approved as Evista for the treatment and prevention of osteoporosis in postmenopausal women, reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis, and reduction in the risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer. Concerning adverse events include:

- Increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE)
- Increased risk of death from stroke

Conjugated estrogens:

- Unopposed conjugated estrogens in postmenopausal women with intact uteri have been associated with the development of endometrial cancer. As endometrial hyperplasia is thought to be a precursor to endometrial cancer, this was closely evaluated as a primary efficacy endpoint in all the longer Phase 3 trials (Trials 303, 304, and 3307).
- The Women's Health Initiative (WHI) estrogen alone substudy reported increased risk of DVT and stroke. The WHI Memory ancillary study (WHIMS) reported increased risk of probable dementia in postmenopausal women age 65 and older. The WHI estrogen plus progestin substudy reported similar risks with the addition of PE, MI, and invasive breast cancer.
- A 2- to 4-fold increased risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogen has been reported.

Cardiovascular disease was evaluated in Trials 303 and 3307 in a similar manner to VTE and cerebrovascular disease. Dementia and cholelithiasis are not specifically discussed in either study report. Breast cancer was reported and evaluated as an AE.

7.3 Major Safety Results

7.3.1 Deaths

Deaths in the CE/BZA clinical development program are shown in Table 109 and listed below. No deaths occurred in Phase 1 or 2 studies. Overall, no concerning pattern of deaths is noted.

Table 109: Deaths in CE/BZA Clinical Program

	CE 0.45/ BZA 20	CE 0.625/ BZA 20	Other CE/BZA 10 mg	Other CE/BZA 40 mg	CE 0.45/ MPA 1.5	BZA 20	Ralox	Placebo
Trial	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
303	0/433	1/414 (0.2)	1/860 (0.1)	2/840 (0.2)			1/423 (0.2)[2]	1/427 (0.2)
3307	0/445	0/474			0/220	0/230		1/474 (0.2)
305	0/127	0/128						0/63
306	0/219	0/218				0/110		0/105
304[1]	0/361	1/349 (0.3)[2]			1/179 (0.6)			1/172 (0.6)
Total	0/1585	2/1583 (0.1)	1/860 (0.1)	2/840 (0.2)	1/399 (0.3)	0/340	1/423 (0.2)	3/1241 (0.2)

Source: Study reviews, appendix
1 Two year data (includes second year extension)
2 Death was reported more than 15 days after withdrawal from the trial
Empty columns denote the specific dose was not studied in the trial

Patients receiving *CE 0.45 mg/BZA 20 mg* in Trial 303:

- None

Patients receiving *CE 0.625 mg/BZA 20 mg:*

- In Trial 303, a 56 year old woman died on Day 631 as a result of a motor vehicle accident
- In trial 304, a 52 year old woman was diagnosed with acute myeloblastic leukemia on Day 364. She discontinued study medication on Day 360 and died six months after her last dose of study medication

Patients receiving *CE 0.45 mg/MPA 1.5 mg:*

- In trial 304, a 48 year-old woman died of an intentional drug overdose on Day 177, 89 days post therapy

Patients receiving *Placebo:*

- In Trial 303, a 53 year old woman with a long smoking history died on Day 342 of an acute exacerbation of COPD
- In Trial 3307 a 53 year old woman with a smoking history was reportedly found dead by her husband on Day 207; no autopsy was performed. The verbatim on the death certificate was arteriosclerosis coronary artery.
- In trial 304 a 51 year old woman receiving placebo died suddenly on Day 660, 125 days post therapy

Patients receiving *Bazedoxifene:*

- None

Patients receiving *Raloxifene:*

- In Trial 303, a 57 year old woman withdrew from the trial on Day 181 and died about Day 270. Pulmonary nodules were known to have been present, but cause of death is unknown. This death was reported more than 15 days after withdrawal from the trial.

Patients receiving *CE 0.625 mg/BZA 10 mg:*

- In Trial 303, a 59 year old woman with a long smoking history discontinued study medicine on Day 494 and died on Day 515 due to intracerebral hemorrhage secondary to metastatic lung cancer

Patients receiving *CE 0.45 mg/BZA 40 mg:*

- In Trial 303, a 52 year old woman died on Day 183 as a result of a small airplane accident

Patients receiving *CE 0.625 mg/BZA 40 mg:*

- In Trial 303, a 52 year old obese woman with hypertension died on Day 642 in her sleep as a result of aspiration. The family refused to provide information beyond the death certificate

No concerning pattern of deaths is noted in the CE/BZA development program.

7.3.2 Nonfatal Serious Adverse Events

Overall serious adverse events reported in the Phase 3 trials are shown in Table 110. The cumulative totals of SAEs for the two doses of CE/BZA to be registered (CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg) and placebo are similar at 4-5%.The most common SOCs were Neoplasms (47 subjects in Phase 3 trials reporting); Injury, Poisoning, and Procedural Complications (22 subjects); and Infections and Infestations (20 subjects). The most common preferred terms were basal cell carcinoma (13 subjects), malignant melanoma (7 subjects), and chest pain, myocardial infarction, non-cardiac chest pain, cholelithiasis, pneumonia, and squamous cell carcinoma of the skin (5 subjects each).

In general in Trial 303, SAEs were present in small numbers, were balanced between treatment groups, and were not markedly higher than placebo or the active raloxifene comparator. From 6 to 8% of subjects in each active treatment group reported a SAE compared to 7% in placebo. In Trial 3307, the incidence of SAE was higher in the CE/MPA group (6%) than the other groups (2-4%). In Trial 304, the incidence of SAE in treatment groups ranged from 4 to 6%. Few SAEs were reported in the small short Trials 305 and 306.

Table 110: Phase 3 Serious Adverse Events in the CE/BZA Clinical Program

	CE 0.45/ BZA 20	CE 0.625/ BZA 20	Other CE/BZA 10 mg	Other CE/BZA 40 mg	CE 0.45/ MPA 1.5	BZA 20	Ralox	Placebo
Trial	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
303	24/433 (6)	23/414 (6)	65/860 (8)	49/840 (6)	N/A	N/A	31/423 (7)	30/427 (7)
3307	16/445 (4)	17/474 (4)			13/220 (6)	5/230 (2)		18/474 (4)
305	2/127 (2)	2/128 (2)						0/63
306	1/219 (<1)	2/218 (1)				1/110 (1)		3/105 (3)
304[1]	22/361 (6)	19/349 (5)			7/179 (4)			7/172 (4)
Total	65/1585 (4)	63/1583 (4)	65/860 (8)	49/840 (6)	20/399 (5)	6/340 (2)	31/423 (7)	58/1241 (5)

Source: Study reviews, appendix
1 Two year data (includes second year extension)
Empty columns denote the specific dose was not studied in the trial

Neoplasms Benign, Malignant, and Unspecified represented the SOC with the most reported SAEs in Trial 303. Overall, neoplasms reported as SAEs were balanced with 11 subjects (3%) in the BZA 10 mg/CE 0.45 mg group, 4 to 7 subjects (1-2%) in other BZA/CE groups, 8 subjects (2%) in the raloxifene group, and 7 subjects (2%) on placebo. The most common preferred term reported was basal cell carcinoma by 1 to 3 subjects (<1 to 1%) in all treatment groups. The next most common preferred terms were combined squamous cell carcinoma (all of the skin) by 0 to 2 subjects (0 to <1%) in all treatment groups. This SOC was also the most commonly reported among SAEs in Trial 3307 (1 to 2% except 3% in the CE/MPA group) and Trial 304(1 to 2% per group), with again basal cell carcinoma and squamous cell carcinoma of the skin being the most common preferred terms, although in Trial 304 as many melanomas were

reported as squamous cell carcinoma (3 subjects, one in the CE 0.625/BZA 20 group and two in the placebo group for melanoma). A fourth squamous cell cancer listed as being of the toenail in Trial 304 may have been a skin cancer as well.

An imbalance of SAEs was noted in the SOC cardiac disorders in Trial 303, with more subjects in the CE 0.625 mg treatment groups reporting SAEs (4 subjects (1%) in the BZA 10 mg/CE 0.625 mg group, 3 subjects (1%) in the BZA 20 mg/CE 0.625 mg group, and 3 subjects (1%) in the BZA 40 mg/CE 0.625 mg group; no more than 1 subject in any other group). In the BZA 10 mg/CE 0.625 mg group, all 4 subjects reported coronary artery disease. In the BZA 20 mg/CE 0.625 mg group, one subject reported CAD and 1 reported myocardial infarction. Women's Health Initiative Studies showed increased risk of non-fatal myocardial infarction with estrogen plus progesterone but not with estrogen alone. This finding was not confirmed in Trial 3307 (1 subject in each CE/BZA group, 3 in placebo with cardiac SOC SAEs) and trial 304 (1 subject in each CE/BZA group, none in placebo with cardiac SOC SAEs).

There were 3 reported SAEs of endometrial hyperplasia in Trial 303 in the BZA 10 mg/CE 0.625 mg group, but the only other case was in placebo. This finding is concerning for lack of endometrial protection with the 10 mg BZA dose.

7.3.3 Dropouts and/or Discontinuations

Adverse events leading to withdrawal in Phase 3 CE/BZA trials are shown in Table 111. The cumulative totals of AEs leading to withdrawal for the two doses of CE/BZA to be registered (CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg) and placebo are similar at 8-10%. The most common SOCs were Musculoskeletal and Connective Tissue Disorders (61 subjects); Vascular Disorders (60 subjects); and Gastrointestinal Disorders (57 subjects). The most common preferred terms were hot flush (37 subjects), headache (21 subjects), and nausea (16 subjects).

In Trial 303, the percentage of subjects withdrawn for AEs was evenly balanced across treatment groups, ranging from 10 to 15% (14% in placebo). Trial 3307 withdrawal for AE was greater in the CE/MPA group at 14% compared to 7-8% in all other groups. Trial 304 withdrawal for AE was also greater in the CE/MPA group at 17% compared to 11-12% in all other groups. Adverse events leading to withdrawal are relatively few in Trials 305 and 306.

Table 111: Adverse Events Leading to Withdrawal in Phase 3 CE/BZA Trials

	CE 0.45/ BZA 20	CE 0.625/ BZA 20	Other CE/BZA	CE 0.45/ MPA 1.5	BZA 20	Ralox	Placebo
Trial	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
303	46/433(11)	52/414(13)	222/1700(13)			59/423(14)	61/427(14)
3307	34/445 (8)	33/474 (7)		31/220(14)	16/230(7)		33/474 (7)
305	5/127 (4)	3/128 (2)					6/63 (10)
306	7/219 (3)	9/218 (4)			8/110 (7)		7/105 (7)
304[1]	39/361(11)	37/349(11)		30/179(17)			20/172(12)
Total	131/1585(8)	134/1583(8)	222/1700(13)	61/399(15)	24/340(7)	59/423(14)	127/1241(10)

Source: Study reviews, appendix
1 Two year data (includes second year extension)
N/A – dose was not evaluated
Empty columns denote the specific dose was not studied in the trial

Although withdrawals for Cardiac SOC events in Trial 303 were generally balanced across treatment groups, withdrawals for coronary artery disease (PT) were limited to the BZA 10 mg/CE 0.625 mg and BZA 20 mg/CE 0.625 mg groups (3 and 2 subjects respectively). A case of angina lead to a withdrawal in the CE 0.625 mg/BZA 20 mg group in Trial 3307, but no coronary artery disease leading to withdrawal was reported. In Trial 304, in the CE 0.45 mg/BZA 20 mg group, a subject withdrew for angina and another for MI, while in the CE 0.625 mg/BZA 20 mg group one subject withdrew for coronary artery disease. A clear pattern is not present.

The Musculoskeletal and Connective Tissue Disease SOC in Trial 303 showed increased withdrawals for the BZA 10 mg/CE 0.45 mg and placebo treatment groups (10 (2%) and 12 (3%) subjects respectively compared to no more than 5 in any other group). For the BZA 10 mg/CE 0.45 mg group, the increase consisted of arthralgia (4 subjects, 1%, no more than 1 in any other group) and back pain (3 subjects, 1%, no more than 1 in any other group) and is likely chance. For placebo, the increase was from osteoporosis (6 subjects, 1%, no more than 2 in any other group) and likely resulted from the lack of a bone-protective agent. No withdrawals for osteoporosis were reported in Trial 3307. In Trial 304, one subject in the CE 0.625 mg/BZA 20 mg and one subject in placebo withdrew for osteoporosis.

The Reproductive System and Breast SOC in Trial 303 showed a marked imbalance in withdrawals with increase in the BZA 10 mg/CE 0.625 treatment group (23 subjects, 5%, no more than 9 (2%) in any other group). This was primarily from an increase in endometrial hyperplasia (11 subjects, 3%, there were also 4 (1%) in the BZA 10 mg/CE 0.45 group but only 1 in all other groups combined) and vaginal hemorrhage (4 subjects, 1%, no more than 2 in any other group). These findings likely resulted from a lack of uterine protective effect of BZA 10 mg. In Trials 3307 and 304, a marked imbalance with increased withdrawals in this SOC occurred in the CE/MPA group with excess vaginal hemorrhage, breast tenderness, and pelvic pain in Trial 3307 and vaginal and uterine hemorrhage in Trial 304.

Vascular SOC withdrawals in Trial 303 appear driven by hot flush withdrawals, which occurred primarily with raloxifene (16 subjects, 4%) and placebo (12 subjects, 3%), although 8 subjects (2%) also withdrew in the BZA 40 mg/CE 0.45 group. Given the population and the raloxifene side effect profile, hot flushes with placebo and raloxifene are expected. It appears the higher dose of bazedoxifene combined with the lower dose of conjugated estrogen may not have as great a tendency to reduce hot flushes as other active dose combinations tested.

In Trial 3307, 3 subjects each in the CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg groups and none in placebo discontinued due to abnormal LFTs. In Trial 303 no excess was found with one withdrawal for abnormal LFTs (several different preferred terms) in each of the CE 0.45 mg/BZA 10 mg, CE 0.45 mg/BZA 20 mg, CE 0.45 mg/BZA 40 mg, CE 0.625 mg/BZA 10 mg, and placebo groups and 3 in the raloxifene group. No cases of withdrawal for LFT abnormalities were reported in Trial 304.

7.3.4 Significant Adverse Events

The crude frequency of severe but non-serious adverse events in the Phase 3 trials on- and post-therapy was calculated. The most frequently reported of these were headache, arthralgia, back pain, pain in extremity, muscle spasms, migraine, hot flush, insomnia, dyspepsia, hypertriglyceridemia, and constipation. In general, these severe adverse events represented about 3 to 4% of adverse events reported and reflected the overall adverse event reports.

7.3.5 Submission Specific Primary Safety Concerns

Venous thromboembolism (VTE): Venous thromboembolism is a known adverse reaction for both estrogen and estrogen agonist/antagonists. In the Women's Health Initiative (WHI) estrogen alone substudy, the relative risk (95% CI) of deep venous thrombosis for conjugated estrogens was 1.47 (1.06, 2.06). For the estrogen plus progestin substudy, the relative risk was 1.95 (1.43, 2.67). (b) (4)

[redacted]

Venous thromboembolism events reported in CE/BZE Phase 3 trials are listed in Table 112. No retinal vein thrombosis was reported in any of the Phase 3 trials. Pulmonary embolism was reported in one subject in Trial 303 in the CE 0.625 mg/BZA 40 mg group (not included in Table 112). No excess of VTE events were seen in the CE/BZA treatment groups.

In the WHI estrogen alone substudy, the DVT rate on CE was 23 per 10,000 woman years compared to 15 for placebo. For the estrogen plus progestin substudy, rates were 26 and 13 per 10,000 woman years, respectively. In Trial 303, considering each treatment group had a mean of 425 subjects with a mean completion rate of 66%, and assuming linear dropout over the 2 years of the study, each treatment group represents about 700 woman years of treatment. Using the lowest placebo rate of 13 per 10,000 woman years, 0.9 events would be expected over the study per treatment group, with up to double that in the active treatment groups. The one DVT event reported in placebo is thus about what is expected. No events being reported in the BZA/CE treatment groups considered for registration is considerably below expectations, as are the two events in the four treatment groups not considered for registration.

Similarly, for Trial 3307, each CE/BZA treatment group and placebo represent about 400 woman years of therapy, with the CE/MPA and BZA monotherapy groups representing about half of that or 200 woman years. About 0.5 DVT events would be expected in placebo, with up to double that in CE/BZA treatment groups and perhaps that number in the CE/MPA and BZA monotherapy groups (due to N about half the size). A single subject in the CE/MPA group with DVT is again below expectations.

In the Multiple Outcomes of Raloxifene (MORE) trial over 2.6 years, venous thromboembolism (VTE, defined as deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) was reported in about 1 in 100 patients treated with raloxifene (rate 38 per 10,000 woman years) which was more than double the placebo rate. The raloxifene group in Trial 303 would be expected to have 2.7 VTE events or more, as VTE events with raloxifene are reportedly more common during the initial months of therapy. No VTE events as defined were reported in this study with raloxifene, which raises concerns for underreporting of VTE events for the combination product as well.

Table 112: Venous Thromboembolism Events Reported in Phase 3 Trials On or Post-therapy

	CE 0.45/ BZA 20	CE 0.625/ BZA 20	Other CE/BZA	CE 0.45/ MPA 1.5	BZA 20	Raloxifene	Placebo
Trial	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Preferred term DVT[1]							
303	0/433	0/414	2/1700 (<1)			0/423	1/427 (<1)
3307	0/445	0/474		1/220 (<1)	0/230		0/474
305	0/127	0/128					0/63
306	0/219	0/218			0/110		0/105
304[2]	3/361 (1)	0/349		0/179			0/172
Total	3/1585 (<1)	0/1583	2/1700 (<1)	1/399 (<1)	0/340	0/423	1/1241 (<1)
Combined preferred terms phlebitis, phlebitis superficial, thrombophlebitis, thrombophlebitis superficial, and venous thrombosis							
303	0/433	1/414 (<1)	13/1700 (1)			2/423 (<1)	2/427 (<1)
3307	1/445 (<1)	0/474		0/220	0/230		0/474
305	0/127	0/128					0/63
306	0/219	0/218			0/110		0/105

	CE 0.45/ BZA 20	CE 0.625/ BZA 20	Other CE/BZA	CE 0.45/ MPA 1.5	BZA 20	Raloxifene	Placebo
Trial	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
304[2]	0/361	0/349		0/179			0/172
Total	1/1585 (<1)	1/1583 (<1)	13/1700 (1)	0/399	0/340	2/423 (<1)	2/1241 (<1)

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response) tables
1 No retinal vein thrombosis was reported in any of the treatment groups in any of the Phase 3 trials. A single case of PE was reported in the CE 0.625 mg/BZA 40 mg group in Trial 303
2 Two year data (includes second year extension)
Empty columns denote the specific dose was not studied in the trial

Coagulation parameters were followed in the Osteoporosis Prevention II Substudy of Trial 303, about 25% of the population. There were not significant changes associated with taking BZA/CE on PT, PTT, protein C, plasminogen activator inhibitor-1 antigen, and D-dimer. Remaining factors affecting fibrinolysis (i.e. plasminogen activity, plasminogen activator inhibitor 1activity) changed in a way which would enhance clot resolution. Fibrinogen, a procoagulant factor, was decreased in all BZA/CE treatment groups. The small differences in antithrombin III and Protein S between the BZA/CE groups and placebo were unlikely to be clinically meaningful.

Four coagulation parameters were measured in Trial 3307: three anti-thrombotic factors (antithrombin III, protein C, protein S) and one pro-thrombotic factor (PAI). Compared to placebo, CE/BZA groups were associated with small but significant declines in antithrombin III, and inconsistent changes in other parameters.

In the Phase 2 trial 203, the following was found for coagulation parameters:

- PTT decreased from baseline a median of from -6.5 to -3.1% in the CE/BZA groups, but this was not statistically different from placebo
- Fibrinogen numerically decreased from baseline, and compared to placebo this was statistically significant for the CE 0.625/BZA 5 and CE 0.625/BZA 20 groups
- Plasminogen activator inhibitor-1activity decreased for the CE 0.625 groups, and for the CE 0.625/BZA 5 and CE 0.625/BZA 20 groups this was statistically significant
- Plasminogen activator inhibitor-1 antigen decreased significantly for the CE 0.625/BZA 5 and CE 0.625/BZA 20 groups but the CE 0.625/BZA 10 group increased numerically more than placebo
- Antithrombin III activity and antithrombin III antigen were reduced with CE/BZA combinations and with CE 0.625, these reductions were significant compared to placebo

Cerebrovascular events: In a trial of postmenopausal women with documented coronary artery disease, an increased risk of death due to stroke was observed during treatment with the estrogen agonist/antagonist raloxifene. In the WHI estrogen-only substudy, and increased risk of stroke was observed. In the bazedoxifene monotherapy trial 301,

based on re-adjudicated data, an increased risk of cerebrovascular events with bazedoxifene therapy was not observed.

Cerebrovascular events were quite uncommon in Trial 303. If only the more definite preferred terms of cerebral hemorrhage, cerebral infarction, CVA, and TIA are considered, 3 events (1%) were reported in the BZA 10 mg/CE 0.625 mg group, no events in the BZA 20 mg/CE 0.625 mg group, 2 events (<1%) in the BZA 40 mg/CE 0.625 mg group, 1 event in the BZA 10 mg/CE 0.45 mg group, 1 event in the BZA 20 mg/CE 0.45 mg group, 1 event in the BZA 40 mg/CE 0.45 mg group, and no events with either raloxifene or placebo. A concern exists for a continued small risk of cerebrovascular disease with the BZA/CE product based on that pattern.

In the WHI estrogen alone substudy, the all stroke rate on CEs was 45 per 10,000 woman years compared to 33 for placebo. For the estrogen plus progestin substudy, rates were 33 and 25 respectively. TIAs were not included. As calculated in the VTE discussion above, each treatment group in Trial 303 represents about 700 woman years of treatment. Using the lowest placebo rate of 25 per 10,000 woman years, 1.8 events would be expected over the study per treatment group, with up to 180% of that (3.2 events) in the active treatment groups. As only three of the BZA/CE groups report single stroke events (others were TIAs) with none reported in placebo, stroke reports were considerably below what would be expected both for BZA/CE treatment groups and placebo (and raloxifene). (Note: On review, possible single stroke events were identified in two other BZA/CE groups).

Low rates of cerebrovascular events were reported in the other Phase 3 trials as well. In Trial 3307, a 54 year old woman receiving BZA 20/CE 0.625 experienced a CVA on study day 83. In Trial 304, one 57 year old woman receiving BZA 20/CE 0.45 (formulation B) reported a transient ischemic attack on study day 18. No cerebrovascular events were reported in Trials 305 and 306.

Cardiac ischemic events: In the WHI estrogen plus progestin substudy, there was an increased risk of coronary artery disease events compared to placebo. No overall difference was seen the in the WHI estrogen-only substudy. No overall difference in cardiovascular events was seen the in the bazedoxifene monotherapy trial 301.

In Trial 303, the Cardiac Disorders SOC was balanced between treatment groups. Although the preferred term of coronary artery disease was confined largely to the CE 0.625 mg treatment groups and especially the BZA 10 mg/CE 0.625 mg group with 4 subjects (1%) in that group reporting events, more angina was reported in the CE 0.45 mg groups (4 subjects across the three groups) and MIs were few and not concentrated in any treatment group, with no more than one per group including one in placebo. A case of coronary artery insufficiency was also reported in the placebo group.

In Trial 3307, a subject in the CE 0.45 mg/BZA 20 mg group and a subject on placebo experienced MI. A subject in the CE 0.45 mg/BZA 20 mg group reported CAD and a subject on placebo reported arteriosclerosis coronary artery. In Trial 304, coronary artery disease events were reported in 2 subjects in the BZA 20/CE 0.45 group, one in the BZA 20 mg/CE 0.625 group, and one in the CE 0.45/MPA 1.5 group. A subject in the BZA 20/CE 0.45 group suffered a myocardial infarction. In Trial 306, a case of angina was reported in the BZA 20 mg/CE 0.625 group and another case in the BZA 20 mg/CE 0.45 group reportedly had cardiac origin ruled out.

Overall, no apparent increase in cardiac risk is noted in these trials.

Neoplasia: The Neoplasm SOC in Trial 303 was balanced between treatment groups with from 4 to 7% of subjects reporting AEs (6% in placebo). For preferred terms, overall little difference was noted between treatment groups. Breast cancer (combined terms) was reported by from 0 to 2 subjects per group (1 subject in placebo). A single case of endometrial cancer was reported in the BZA 20 mg/CE 0.45 mg group and a uterine neoplasm in the BZA 10 mg/CE 0.45 mg group. A case of ovarian cancer was reported in the BZA 40 mg/CE 0.625 mg group and a case of ovarian epithelial cancer in the BZA 10 mg/CE 0.45 mg group.

In Trial 3307, the CE/MPA group had a mild excess of subjects in the SOC neoplasms (benign and malignant) of 6.4% compared to 2.1% - 2.7% for the other groups. This is attributable to slightly greater numbers of CE/MPA subjects with AEs of uterine leiomyoma (fibroid) and other benign neoplasms, and basal cell Ca. The CE/BZA groups were similar to placebo in incidence of various neoplasms. During the trial, 2 subjects in the CE 0.45 mg/BZA 20 mg group and one each in the CE 0.45 mg/MPA group and the placebo group developed breast cancer. No gynecologic malignancies were reported.

During the two years of trial 304, 40 subjects reported at least one neoplasm adverse event (14 in the BZA 20/CE 0.45, 13 in the BZA 20 mg/CE 0.625 group, 5 in the CE 0.45/MPA 1.5 group, and 8 in the placebo group). The most commonly reported event was uterine leiomyoma, reported in 16 subjects with more reports in the bazedoxifene/estrogen groups (7 in the BZA 20/CE 0.45, 5 in the BZA 20 mg/CE 0.625 group, 2 in the CE 0.45/MPA 1.5 group, and 2 in the placebo group). Reported malignant neoplasms were predominantly of skin origin – malignant melanoma (3 subjects), basal cell carcinoma (5 subjects), and squamous cell carcinoma of the skin (3 subjects). No breast or gynecologic malignancies were reported.

In Trial 306 a case of breast cancer was reported in the BZA 20 mg/CE 0.45 treatment group and a squamous cell carcinoma of the skin was reported in the BZA 20 mg treatment group. No uterine malignancies were reported.

Reproductive disorders: Reproductive tissues are the prime target for both estrogens and estrogen agonist/antagonists.

In Trial 303, breast adverse events appeared generally balanced between treatment groups. Breast pain was the most common adverse event with from 2 to 6 % of subjects per group reporting this (placebo 4%). Breast pain was also a secondary efficacy endpoint and showed no difference between the BZA/CE groups and either placebo or raloxifene. Mammogram abnormal was the next most common AE with from 8 to 15 subjects (2-3%) in the CE/BZA groups reporting this compared to 6 subjects (1%) in placebo (on-treatment mammograms were done at Months 12 and 24). Fibrocystic breast disease may have been slightly more common in the BZA/CE groups (0 to 3 subjects, 0-1%, no subjects with raloxifene or placebo).

In Trial 3307, breast tenderness was the most commonly reported AE, with an excess of 11% of subjects reporting that in the CE/MPA group and from 2 to 4% in other groups. Mammogram abnormal was similar between groups (3 subjects in the CE 0.45/BZA 20 mg group, one each in the CE 0.625/BZA 20 mg, CE 0.45/MPA, and placebo groups). Mammograms were done at Screening and Month 12.

In Trial 304, adverse events relating to the breast were reported by 95 subjects (31 in the BZA 20/CE 0.45, 24 in the BZA 20 mg/CE 0.625 group, 29 in the CE 0.45/MPA 1.5 group, and 11 in the placebo group). The most common adverse event was breast or nipple pain, discomfort or tenderness which was reported by 25 subjects in the BZA 20/CE 0.45, 22 subjects in the BZA 20 mg/CE 0.625 group, 23 subjects in the CE 0.45/MPA 1.5 group, and 6 subjects in the placebo group. Fibrocystic breast disease and related changes (i.e., mammarian dysplasia) was reported by eight subjects (4 in the BZA 20/CE 0.45, 2 in the BZA 20 mg/CE 0.625 group, one in the CE 0.45/MPA 1.5 group, and one in the placebo group).

In Trial 303, the Reproductive System and Breast Disorder SOC showed increased events in the bazedoxifene 10 mg treatment groups (36% in the BZA 10 mg/CE 0.625 mg group, 33% in the BZA 10 mg/CE 0.45 mg group, 21-27% other active treatment groups, 27% placebo). Particularly contributing to this difference were vaginal hemorrhage (6% in the BZA 10 mg/CE 0.625 mg group, 5% in the BZA 10 mg/CE 0.45 mg group, <1-3% other active treatment groups, 2% placebo), endometrial hyperplasia (5% in the BZA 10 mg/CE 0.625 mg group, 2% in the BZA 10 mg/CE 0.45 mg group, 0-<1% other active treatment groups, <1% placebo), vaginal discharge (4% in the BZA 10 mg/CE 0.625 mg group, 4% in the BZA 10 mg/CE 0.45 mg group, 1-3% other active treatment groups, 2% placebo), and genital discharge (8% in the BZA 10 mg/CE 0.625 mg group, 8% in the BZA 10 mg/CE 0.45 mg group, 5-7% other active treatment groups, 6% placebo). Vulvovaginal pruritis was also increased in the raloxifene group (4% in the BZA 10 mg/CE 0.625 mg group, 5% in the BZA 10 mg/CE 0.45 mg group, 1-2% other BZA/CE groups, 4% raloxifene group, 3% placebo). These findings were likely largely secondary to lack of uterine protective effect with bazedoxifene 10 mg.

Uterine polyps were more common in all conjugated estrogen treatment groups except the BZA 40 mg/CE 0.45 mg group (BZA 40 mg/CE 0.45 mg group 2 subjects (<1%), other BZA/CE groups 4-11 subjects (1-3%), Raloxifene no subjects, placebo 2 subjects (<1%)). Uterine polyps have been associated with estrogen use.

Ultrasound uterus abnormal was reported most commonly in Trial 303 in the bazedoxifene 10 with conjugated estrogen groups (10 subjects (2%) in the BZA 10 mg/CE 0.625 mg group, 3 subjects (1%) in the BZA 20 mg/CE 0.625 mg group, no subjects in the BZA 40 mg/CE 0.625 mg group, 7 subjects (2%) in the BZA 10 mg/CE 0.45 mg group, 5 subjects (1%) in the BZA 20 mg/CE 0.45 mg group, 1 subject (<1%) in the BZA 40 mg/CE 0.45 mg group, no subjects in the raloxifene group, 1 subject (<1%) in the placebo group). This is again consistent with a lack of uterine protection with 10 mg bazedoxifene.

In Trial 3307, AEs related to gynecologic bleeding were much more commonly reported in the CE/MPA group (18.2%, vs. 2.5-5.2% in the other groups). Other uterine AEs (adenexal pain, uterine cyst/ polyp/ prolapse) were non-serious, infrequent and did not show appreciable treatment group differences. Incidence of vulvovaginal candidiasis/ mycotic infection was greater with CE/MPA (3.2%) than placebo (0.6%); incidence with CE/BZA was intermediate (1.1-2.5%).

In Trial 304, adverse reactions relating to the uterus, vulva, or vagina were reported by 211 subjects (57 in the BZA 20/CE 0.45, 71 in the BZA 20 mg/CE 0.625 group, 63 in the CE 0.45/MPA 1.5 group, and 20 in the placebo group). Uterine or vaginal bleeding events were reported by 104 subjects, with an imbalance in the active control CE 0.45/MPA 1.5 group (25%) as compared to 6 – 8% in the BZA/CE groups and 5% in the placebo group. Endometrial adverse events were reported in 37 subjects, predominantly in the BZA 20 mg/CE 0.625 group (6% compared to 1 – 4% in the other treatment groups). The most commonly reported endometrial adverse event was endometrial hypertrophy.

Because of (b) (4) Formulation B and Formulation C in this trial, the reviewer evaluated uterine and vaginal adverse events by Year. All subjects began the study on Formulation B, with an average number of days on Formulation B was 207 days with a range of 7 days to 367 days. During the second year of the trial, all subjects received Formulation C (b) (4)

Fractures: Fractures were collected as adverse events in Trial 303. No scheduled spine or other x-rays were done. The population consisted of women age 40 to 75 at least 12 months postmenopausal. In addition, about 40% of the population were greater than 5 years postmenopausal, had a lumbar spine or total hip T-score of -1.0 to -2.5, and had at least one other risk factor for osteoporosis. Another approximately 25% of the population was between 1 and 5 years postmenopausal and had at least one other risk factor for osteoporosis.

Fractures were generally balanced between groups (2-4%, 3% placebo). The isolated increase in hand fractures in the BZA 10 mg/CE 0.45 mg group was likely a chance occurrence. The BZA 10 mg/CE 0.45 mg group overall showed one of the larger increases in BMD at the lumbar spine, total hip, and distal radius, so loss of BMD was probably not involved. This trial was not designed to evaluate fracture risk.

Fractures in Trial 3307, which were collected as regular AEs, occurred in 1.7% of subjects overall, with no appreciable difference between groups.

In Trial 304, three subjects reported fracture: two subjects with ankle fracture and one subject with tibial fracture, all in the BZA 20/CE 0.45 group. One subject in the placebo group did sustain a cervical vertebral and rib fracture as well as traumatic lung injury and concussion due to a traffic accident.

Ocular: The Bazedoxifene non-US label postmarketing section was updated in 2012 to include ocular events and the effects on the ability to drive. Ocular events seem to be prominent in the most recent PSURs, increasing from 11.6% to 13.8% between the last two and occurred predominantly (70%) in the elderly (> age 65). The events are generally nonspecific (blurred vision, visual acuity reduced, visual impairment, eye pain) with isolated events of retinal vein occlusion (1), sudden visual loss (1), and retinal vein thrombosis (2).

In Trial 303 the Eye Disorder SOC showed increased events in placebo (43 subjects (10%), 20 to 35 subjects in other treatment groups) which on review consisted of small increases in several mostly unrelated preferred terms (especially cataract, lacrimation increased, ocular hyperemia, and vitreous floaters). Preferred terms related to blindness and visual impairment were relatively uncommon and generally distributed between treatment groups. A similar general pattern was seen in Trial 304 with 7% of subjects on placebo reporting Eye SOC AEs compared to 4-6% in the other treatment groups. In Trial 3307, 2-4% of subjects reported Eye SOC AEs across treatment groups.

Gallbladder disease: A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported with conjugated estrogens.

In the Phase 3 trials for CE/BZA, adverse events related to the gallbladder were reported by 18 subjects (1.1%) on CE 0.45/BZA 20, 7 subjects (0.4%) on CE 0.625/BZA 20, and 8 subjects (0.6%) on placebo. These adverse events included biliary colic, cholecystitis, cholelithiasis, and gallbladder polyp. There does not appear to be an increase in gallbladder related adverse events in the CE/BZA groups of these trials.

Dementia: In the Women's Health Initiative Memory Study (WHIMS), when data were pooled from the estrogen only and estrogen plus progestin populations as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. The population ranged from 65 to 79 years of age. It is unknown whether these findings apply to younger postmenopausal women.

There were no reports of dementia disorders in any of the Phase 3 CE/BZA trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

On- and post-treatment adverse events combined for Trials 303 and 3307 which occurred in at least 5% of subjects in a treatment group are shown in Table 113. Doses of bazedoxifene in the combination product not considered for registration (10 and 40 mg in Trial 303) are not included, but active comparators (raloxifene from Trial 303, CE 0.45 mg/medroxyprogesterone 1.5 mg and BZA 20 mg monotherapy from Trial 3307) are included. Calculations are done using only the listed CE/BZA and placebo treatment groups, as these were in both trials in approximately equal numbers, and are therefore more appropriately combinable, as Trial 303 was two years and 3307 only one year in duration.

In Trial 303, 433 subjects were randomized to CE 0.45 mg/BZA 20 mg, 414 subjects were randomized to CE 0.625 mg/BZA 20 mg, and 427 subjects were randomized to placebo. Of these, 78%, 77%, and 73% completed one year and 69%, 68%, and 64% completed 2 years respectively. In Trial 3307, 445 subjects were randomized to CE 0.45 mg/BZA 20 mg, 474 subjects were randomized to CE 0.625 mg/BZA 20 mg, and 474 subjects were randomized to placebo. Of these, 80%, 83%, and 81% completed one year respectively.

In general, adverse events were similar between treatment groups. Any adverse event was reported by from 90 to 92% of subjects in the considered arms. The SOCs with the largest number of events were Infections and Infestations (overall 54% of subjects reporting), Musculoskeletal and Connective Tissue Disorders (51%), Gastrointestinal Disorders (39%), and Nervous System Disorders (39%). The most common PTs were headache (overall 30% of subjects reporting), back pain (20%), arthralgia (20%), nasopharyngitis (16%), pain in extremity (13%), influenza (13%), and myalgia (11%).

A trend of more GI SOC adverse events with CE/BZA is noted (44% of subjects with CE 0.45/BZA 20, 38% CE 0.625/BZA 20, 36% placebo).Increases with several preferred terms seem to account for this increase (abdominal pain, abdominal pain upper, diarrhea, nausea).

A trend of more Respiratory SOC adverse events with CE/BZA is noted (23% of subjects with CE 0.45/BZA 20, 20% CE 0.625/BZA 20, 18% placebo). Increases with several preferred terms seem to account for this increase (oropharyngeal pain, nasal congestion, rhinitis seasonal, sinus congestion, upper respiratory tract congestion).

A trend of more Skin and Subcutaneous Tissue SOC adverse events with CE/BZA is noted (18% of subjects with CE 0.45/BZA 20, 18% CE 0.625/BZA 20, 15% placebo). Increased alopecia (3% of subjects with CE 0.45/BZA 20, 3% CE 0.625/BZA 20, 1% placebo) and dry skin (2% of subjects with CE 0.45/BZA 20, 2% CE 0.625/BZA 20, 1% placebo) with CE/BZA seem to be primarily responsible. Urticaria was reported by 11 subjects (1%) with CE 0.45/BZA 20, 8 subjects (1%) with CE 0.625/BZA 20, and 3 subjects (<1%) with placebo.

The Reproductive System and Breast Disorder SOC showed similar percentages of subjects with AEs between groups (24% of subjects with CE 0.45/BZA 20, 23% CE 0.625/BZA 20, 23% placebo).

The preferred term nasopharyngitis was more frequently reported in the CE/BZA arms (19% of subjects with CE 0.45/BZA 20, 16% CE 0.625/BZA 20, 14% placebo). The preferred term muscle spasm was more frequently reported in the CE/BZA arms (11% of subjects with CE 0.45/BZA 20, 8% CE 0.625/BZA 20, 6% placebo). Hot flushes were reported in similar percentages of subjects (5% of subjects with CE 0.45/BZA 20, 6% CE 0.625/BZA 20, 7% placebo). Triglycerides increased (4% of subjects with CE 0.45/BZA 20, 3% CE 0.625/BZA 20, 2% placebo) and hypertriglyceridemia (4% of subjects with CE 0.45/BZA 20, 4% CE 0.625/BZA 20, 3% placebo) were also reported in similar percentages of subjects.

Table 113: On- and Post-treatment Adverse Events in Trials 303 and 3307 Reported by at least 5% of Subjects in a Treatment Group

SOC PT[1]	CE 0.45/ BZA 20	CE 0.625/ BZA 20	CE 0.45/ MPA 1.5	BZA 20	Ralox	Placebo
	N=878	N=888	N=220	N=230	N=423	N=901
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	805 (92)	807 (91)	192 (87)	198 (86)	400 (95)	812 (90)
Ear & labyrinth	58 (7)	58 (7)	6 (3)	6 (3)	33 (8)	53 (6)
Eye	44 (5)	51 (6)	5 (2)	4 (2)	20 (5)	55 (6)
GI	385 (44)	338 (38)	69 (31)	73 (32)	215 (51)	327 (36)
A. pain	73 (8)	68 (8)	11 (5)	11 (5)	41 (10)	58 (6)

SOC PT[1]	CE 0.45/ BZA 20	CE 0.625/ BZA 20	CE 0.45/ MPA 1.5	BZA 20	Ralox	Placebo
	N=878	N=888	N=220	N=230	N=423	N=901
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
A. pain upper	77 (9)	72 (8)	8 (4)	7 (3)	46 (11)	56 (6)
Constipation	53 (6)	52 (6)	13 (6)	14 (6)	43 (10)	46 (5)
Diarrhea	74 (8)	54 (6)	11 (5)	10 (4)	37 (9)	48 (5)
Dyspepsia	74 (8)	44 (5)	11 (5)	8 (3)	43 (10)	53 (6)
Nausea	78 (9)	60 (7)	11 (5)	8 (3)	26 (6)	50 (6)
Toothache	42 (5)	30 (3)	8 (4)	8 (3)	23 (5)	34 (4)
Gen & ad site	192 (22)	203 (23)	28 (13)	34 (15)	132 (31)	201 (22)
Chest pain	22 (3)	23 (3)	0	0	30 (7)	23 (3)
Fatigue	41 (5)	37 (4)	4 (2)	6 (3)	25 (6)	41 (5)
Edema periph	44 (5)	31 (3)	3 (1)	3 (1)	28 (7)	39 (4)
Pain	46 (5)	50 (6)	6 (3)	14 (6)	25 (6)	40 (4)
Immune system	62 (7)	56 (6)	8 (4)	6 (3)	32 (8)	46 (5)
Infect & infest	500 (57)	473 (53)	98 (45)	99 (43)	256 (61)	475(53)
Influenza	123 (14)	103 (12)	11 (5)	17 (7)	96 (23)	113 (13)
Nasopharyng	166 (19)	140 (16)	27 (12)	41 (18)	61 (14)	124 (14)
Sinusitis	71 (8)	81 (9)	12 (5)	15 (7)	40 (9)	76 (8)
URI	86 (10)	80 (9)	10 (5)	8 (3)	58 (14)	75 (8)
UTI	69 (8)	58 (7)	5 (2)	12 (5)	37 (9)	66 (7)
Injury,pois,comp	136 (15)	146 (16)	37 (17)	34 (15)	87 (21)	168 (19)
Procedural pain	20 (2)	35 (4)	13 (6)	2 (1)	16 (4)	26 (3)
Investigations	190 (22)	189 (21)	30 (14)	22 (10)	140 (33)	182 (20)
TG increased	33 (4)	26 (3)	4 (2)	3 (1)	22 (5)	20 (2)
PAP abn	24 (3)	23 (3)	2 (1)	0	23 (5)	17 (2)
Wt increased	38 (4)	38 (4)	8 (4)	5 (2)	27 (6)	43 (5)
Metab & nutrit	85 (10)	78 (9)	10 (5)	12 (5)	67 (16)	87 (10)
Hyperchol	27 (3)	37 (4)	3 (1)	4 (2)	33 (8)	39 (4)
HyperTG	34 (4)	32 (4)	0	2 (1)	27 (6)	24 (3)
MS & CT	444 (51)	460 (52)	76 (35)	84 (37)	271 (64)	455 (50)
Arthralgia	164 (19)	175 (20)	18 (8)	19 (8)	139 (33)	186 (21)
Back pain	175 (20)	193 (22)	19 (9)	26 (11)	121(29)	172 (19)
Muscle spasms	95 (11)	70 (8)	14 (6)	22 (10)	38 (9)	55 (6)
Myalgia	105 (12)	98 (11)	12 (5)	17 (7)	75 (18)	94 (10)
Neck pain	50 (6)	50 (6)	6 (3)	8 (3)	40 (9)	43 (5)
Pain in extrem	122 (14)	114 (13)	29 (13)	15 (7)	80 (19)	123 (14)
Neoplasm	41 (5)	32 (4)	14 (6)	6 (3)	24 (6)	37 (4)
Nervous system	335 (38)	332 (37)	71 (32)	60 (26)	207 (49)	375 (42)
Dizziness	52 (6)	34 (4)	8 (4)	6 (3)	23 (5)	32 (4)
Headache	242 (28)	265 (30)	51 (23)	44 (19)	170 (40)	282 (31)
Psychiatric	164 (19)	158 (18)	21 (10)	26 (11)	121 (29)	170 (19)
Anxiety	32 (4)	40 (5)	7 (3)	3 (1)	30 (7)	34 (4)
Depression	50 (6)	52 (6)	5 (2)	6 (3)	38 (9)	47 (5)
Insomnia	72 (8)	54 (6)	11 (5)	15 (7)	55 (13)	87 (10)
Renal & urinary	55 (6)	61 (7)	6 (3)	8 (3)	42 (10)	67 (7)
Repro & breast	209 (24)	202 (23)	82 (37)	37 (16)	89 (21)	209(23)
Breast tender	19 (2)	20 (2)	25 (11)	5 (2)	0	15 (2)
Gen discharge	23 (3)	26 (3)	0	0	27 (6)	27 (3)

SOC PT[1]	CE 0.45/ BZA 20	CE 0.625/ BZA 20	CE 0.45/ MPA 1.5	BZA 20	Ralox	Placebo
	N=878	N=888	N=220	N=230	N=423	N=901
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vag hemorrha	38 (4)	25 (3)	34 (15)	13 (6)	2 (<1)	38 (4)
Resp,thor,media	203 (23)	178 (20)	44 (20)	31 (13)	114 (27)	166 (18)
Cough	65 (7)	65 (7)	11 (5)	9 (4)	40 (9)	65 (7)
Orophar pain	69 (8)	65 (7)	20 (9)	11 (5)	46 (11)	54 (6)
Skin & subcut	161 (18)	160 (18)	40 (18)	33 (14)	78 (18)	135 (15)
Vascular	112 (13)	126 (14)	17 (8)	24 (10)	81 (19)	131 (15)
Hot flush	40 (5)	51 (6)	11 (5)	20 (9)	31 (7)	63 (7)
Hypertension	57 (6)	51 (6)	5 (2)	3 (1)	31 (7)	52 (6)

Source: NDA022247, GSR 0000, 5.3.5.1 (original NDA) and GSR 0007, 5.3.5.1 (Information request response) datasets, reviewer analysis
1 MedDRA version 15.1

7.4.2 Laboratory Findings

For laboratory abnormalities reported as adverse events for Trial 303, the preferred terms aspartate aminotransferase increased and alanine aminotransferase increased were more often reported in the raloxifene group. There did not appear to be a tendency for these preferred terms to be more common with the combination product. Blood cholesterol increased was reported most commonly in the placebo group. Hypercholesterolemia was reported in similar percentages of subjects across treatment groups. The preferred terms hypertriglyceridemia and triglycerides increased were generally more common with the combination product than placebo (6 to 9% of combination product groups, 6% in placebo and 4 to 6% of combination product groups, 4% placebo respectively).

Laboratory values of potential clinical importance in Trial 303 were predetermined. In general, the number of subjects with specific laboratory events of potential clinical significance was similar between treatment groups. Total bilirubin increase >1.7 mg/dL was more common in the placebo group. AST increase >50% above normal range was similar between groups. ALT increase > 2 times ULN was highest in the raloxifene group. Cholesterol increase >50 mg/dL to >200 mg/dL was more common in the placebo group. Triglyceride increase >50 mg/dL to >250 mg/dL was more common in the combination product group and raloxifene group (88 subjects (22%) in placebo, 119-148 subjects (30-38%) in combination product treatment groups, and 116 subjects (30%) in raloxifene).

In Trial 303, combined bazedoxifene/conjugated estrogen and raloxifene were associated with mild mean decreases in total cholesterol from Baseline to Month 24 (cholesterol -9 to -14 mg/dL for combination drug, -7 mg/dL for raloxifene against placebo). Slight increases in triglycerides were noted (1 to 19 mg/dL for the active treatment groups against placebo). ALT and AST in active treatment groups were

essentially unchanged compared to placebo. Alkaline phosphatase was reduced 12 to 16 U/L with active treatment compared to placebo, probably due to antiresorptive bone effect. Total bilirubin showed a statistically but probably not clinically significant reduction of -0.1 mg/dL in all treatment groups. Bazedoxifene/conjugated estrogen and raloxifene were associated with slight mean decreases from Baseline to Month 24 in calcium (-0.1 to -0.2 mg/dL for active drug, no change for placebo) and phosphate (-0.2 to -0.3 mg/dL for active drug, no change for placebo).

Lipid parameters were followed in the Osteoporosis Prevention II Substudy of Trial 303, about 25% of the population. The effect of the lipid profile on arthrosclerosis would be expected to improve with BZA/CE based on HDL cholesterol level increase, LDL cholesterol level decrease, apolipoprotein A1 level increase, and lipoprotein (a) level decrease. Triglyceride level increase may have a deleterious effect (6 to 19% compared to placebo).

Coagulation parameters were also followed in the Osteoporosis Prevention II Substudy of Trial 303. See 7.3.5 under VTE and the study review in the appendix for that information. Plasma homocysteine levels with CE/BZA decreased over 24 months numerically more than placebo. This was statistically significant for the CE 0.625/BZA40 and CE 0.45/BZA 10 groups.

In Trial 3307, 8 subjects experienced LFT elevation which contributed, at least in part, to discontinuation of treatment: 3 (1%) with CE 0.45/BZA 20, 3 (1%) with CE 0.625/BZA 20, 1 (<1%) with CE/MPA, and 1 (<1%) with placebo. Consistent with anti-bone-resorptive effects of estrogens and SERMs, there were small, statistically significant decreases from baseline in serum alkaline phosphatase for all 4 active treatment groups compared to placebo, and in serum calcium and phosphorus for both CE/BZA groups compared to placebo. CE/BZA groups showed significant declines in mean serum bilirubin and ALT relative to baseline and placebo; mean AST showed essentially no change in any group. CE/BZA groups, relative to placebo, had small but significant decreases in mean serum creatinine, BUN, glucose, total and LDL cholesterol; and significant increases in HDL cholesterol and triglycerides. See 7.3.5 under VTE and the study review in the appendix for coagulation parameter information.

In Trial 304, laboratory adverse events were reported by 46 subjects. The most common adverse events reported were blood cholesterol increased and blood triglycerides increased. Clinically important laboratory findings were identified in 8 subjects, predominantly elevation of total cholesterol or triglycerides or both. Triglyceride elevation was in groups treated with conjugated estrogen. No clinically important mean changes in laboratory values were noted.

7.4.3 Vital Signs

A total of 329 subjects were reported as having AEs of hypertension during Trial 303: 32-49 subjects (9-11%) in the CE/BZA groups, 31 subjects (7%) in the raloxifene group, and 42 subjects (10%) in placebo). A total of 52 subjects were reported as having AEs of hypertensive crisis during the study: 4-9 subjects (1-2%) in the CE/BZA groups, 5 subjects (1%) in the raloxifene group, and 7 subjects (2%) in placebo). A potentially clinically important increase from baseline of systolic BP was defined as ≥ 20 mm Hg increase with absolute value of ≥ 160 mm Hg. This occurred on-therapy in 235 subjects: 25-36 subjects (6-9%) in the CE/BZA groups, 34 subjects (9%) in the raloxifene group, and 20 subjects (5%) in placebo. A clinically important increase from baseline of diastolic BP was defined as ≥ 15 mm Hg increase with absolute value ≥ 90 mm Hg. This occurred on-therapy in 347 subjects: 41-46 subjects (10-11%) in the CE/BZA groups, 43 subjects (10%) in the raloxifene group, and 43 subjects (10%) in placebo. Mean change in systolic and diastolic blood pressure over the 24 months of the study was small and not different from placebo. Systolic blood pressure changed by a mean of 0.0 to 2.1 mmHg in the BZA/CE treatment groups compared to placebo with 0.8 mmHg change in the raloxifene treatment group. Diastolic blood pressure changed by a mean of -0.5 to 0.9 mmHg in the BZA/CE treatment groups compared to placebo with -0.6 mmHg change in the raloxifene treatment group. Significant blood pressure increase was not seen with the bazedoxifene/conjugated estrogen in this study.

In Trial 303, weight increased was reported as an adverse event in 20 to 27 subjects (5-6%) in the BZA /CE treatment groups, 27 subjects (6%) in the raloxifene treatment group, and 21 subjects (5%) in the placebo group. A potentially clinically important weight gain of ≥ 15% and ≥ 25 pounds over the course of the study was reported in 1 to 7 subjects (<1-2%) in the BZA /CE treatment groups, 5 subjects (5%) in the raloxifene treatment group, and 4 subjects (1%) in the placebo group. Weight changed by a mean compared to placebo of -0.45 to 0.17 kg in the BZA /CE treatment groups and 0.29 kg in the raloxifene treatment group. No significant weight change was noted with the BZA/CE combination.

In Trial 3307, the number of subjects with BP increases of potential significance was slightly greater with CE/BZA or CE/MPA compared to placebo, consistent with known potential of estrogen treatment. There were slightly more placebo subjects with weight gain (≥15% and ≥25 lb.), compared to the other groups. Mean changes in BP and weight were not statistically different between groups.

In Trial 304, across the two year study, clinically important changes in vital signs (increased systolic blood pressure, diastolic blood pressure, or both) were noted in 10 subjects (4 in the BZA 20/CE 0.45, 2 in the BZA 20 mg/CE 0.625 group, 4 in the CE 0.45/MPA 1.5 group, and none in the placebo group). No subjects were withdrawn from the study due to vital sign changes.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed at Screening and Month 24 or early termination in Trial 303. ECG values of potential clinical importance occurring during the study were defined as:

- Heart rate increase of ≥15 beats/min and ≥120 beats/min
- Heart rate decrease of ≥15 beats/min and ≤50 beats/min
- PR interval ≥200 msec
- QT interval ≥480 msec
- QTc > 470 msec (females) or increase of ≥60 msec
- QRS interval ≥120 msec
- Rhythm any rhythm other than sinus rhythm
- Overall evaluation any evaluation other than normal

The total ECG events and most individual events were balanced between groups. The event QT interval ≥480 msec occurred in more subjects in the raloxifene group (6 subjects, 2%) and most BZA/CE groups (1-8 subjects, <1-3%) compared to placebo (1 subject, <1%), but this was not maintained with the QTc > 470 msec (females) or increase of ≥60 msec event (active treatment groups 9-18 subjects, 3-6%, placebo 10 subjects, 4%).

In Trial 3307, there were 6 subjects (two in each CE/BZA group, two in placebo) with various types of ECG abnormalities of “potential clinical importance” with cardiologist referral; none resulted in major therapeutic interventions.

Electrocardiograms (ECGs) in Trial 304 were collected at baseline, month 12, and month 24. Over the two years of the study, 16 subjects had abnormal ECG findings of potential clinical importance (7 in the BZA 20/CE 0.45, 4 in the BZA 20 mg/CE 0.625 group, 3 in the CE 0.45/MPA 1.5 group, and 2 in the placebo group). These subjects records were further reviewed in a blinded manner. Overall, five subjects were found to have clinically important ECG changes:

- A 53yo receiving BZA 20/CE 0.45 was noted to have abnormal t wave changes on the month 24 ECG. No abnormalities were noted on nuclear stress test.
- A 51yo receiving BZA 20/CE 0.45 was noted to have first degree AV block and bradycardia on the month 24 ECG. No abnormalities were on stress test or echocardiogram.
- A 53yo receiving BZA 20/CE 0.45 was noted to have ST-T wave abnormalities and possible left ventricular hypertrophy on the month 12 ECG. The subject was referred to her primary care physician and no further evaluation was done.
- A 54yo receiving BZA 20 mg/CE 0.625 was noted to have a possible old infarct on month 24 ECG. Work-up was negative.

- A 52yo receiving CE 0.45/MPA 1.5 was noted to have sinus bradycardia and ST-T wave changes at month 12. Work-up was negative for ischemic disease.

A definitive QT study for bazedoxifene was performed (b) (4)
At the doses tested (20 mg and 120 mg bazedoxifene acetate) the study was negative. The clinical pharmacology reviewer did not perform additional concentration-QTc analysis due to the negative findings using the ICH guidance approach. The review team performed the ICH E 14 primary analyses independently and the findings were consistent with those reported by the Applicant.

No thorough QTc study has been done for conjugated estrogens, however conjugated estrogens have been used extensively for many decades without a safety signal emerging.

7.4.5 Special Safety Studies/Clinical Trials

Transvaginal Ultrasound: Transvaginal ultrasounds were performed to assess endometrial thickness, ovarian volume and the presence of ovarian cysts. In all studies, scans were performed by qualified technologists and read locally by board certified or eligible gynecologists or radiologists.

In Trial 303, transvaginal ultrasonography was performed at screening, month 12 and month 24 at approximately one-third of study sites. Mean change from baseline was reported at both time points. As outlined in Table 114 below, there is a bazedoxifene dose dependent response for endometrial thickness. The products containing 10 mg bazedoxifene are associated with increased endometrial thickness at both 12 and 24 months when compared to placebo.

Table 114: Trial 3115A1-303: TVU – Mean Change From Baseline in Endometrial Thickness

	CE0.625/ BZA 10 N=430	CE0.625/ BZA 20 N=414	CE0.625/ BZA 40 N=417	CE0.45 BZA 0 N=430	CE0.45 BZA20 N=433	CE0.45 BZA40 N=423	ralox N=423	placebo N=427
Month 12								
N, pairs	121	111	106	117	119	112	109	104
Mean (mm)	2.54	0.62	0.40	1.23	0.50	0.34	0.37	0.37
SE	0.20	0.21	0.21	0.20	0.20	0.20	0.21	0.21
Month 24								
N, pairs	105	101	94	100	110	100	95	85
Mean (mm)	2.15	0.45	0.14	1.91	0.56	0.03	0.16	0.02
SE	0.24	0.24	0.25	0.24	0.23	0.24	0.25	0.26

Source: CSR 64104, table 10-46

TVU findings were also evaluated categorically and are summarized in the table below using the following reference criteria

- endometrial thickness
  - absolute value > 5mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

As outlined in Table 115 below, there is evidence of a bazedoxifene dose dependent response for endometrial thickness. The products containing 10 mg bazedoxifene were associated with an increased number of subjects with absolute values of endometrial thickness above 5 mm and 8 mm and increases from baseline greater than 3 mm and 5 mm.

Table 115: Trial 3115A1-303: TVU – Categorical Changes In Endometrial Thickness

	0.625/ BZA 10 N=430	**0.625/ BZA 20** N=414	**0.625/ BZA 40** N=417	**0.45/ BZA 10** N=430	**0.45/ BZA 20** N=433	**0.45/ BZA 40** N=423	**ralox** N=423	**plac** N=427
Subjects with scans, N	137	119	113	127	128	119	118	114
Endometrial thickness								
value > 5mm	59 (43)	18 (15)	11 (10)	36 (28)	18 (14)	8 (7)	14 (12)	9 (8)
value > 8mm	35 (26)	4 (3)	3 (3)	18 (14)	5 (4)	0	2 (2)	4 (4)
increase > 3mm	49 (36)	13 (11)	6 (5)	28 (22)	15 (12)	6 (5)	5 (4)	5 (4)
increase > 5mm	33 (24)	4 (3)	3 (3)	15 (12)	7 (6)	1 (1)	1 (1)	4 (4)
Ovarian volume increase ≥ 2 cm^3	17 (16)	13 (14)	10 (11)	10 (10)	11 (11)	9 (9)	14 (15)	7 (8)
Ovarian cysts	12 (11)	6 (6)	12 (12)	16 (15)	11 (11)	9 (9)	8 (8)	14 (14)

Source: CSR 64104, tables 10-47, 10-48, 15-126

In Trial 3307, transvaginal ultrasonography was performed at screening and month 12. Mean change in endometrial thickness was evaluated at month 12. Categorical criteria were used to determine potentially clinically important abnormalities. The records for subjects with potentially clinically important abnormalities were then reviewed in a blinded manner to determine those subjects with clinically important findings. The criteria used for determining scans of potential clinical importance were the following:

- endometrial thickness
  - absolute value > 4mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

As outlined in Table 116 below, mean endometrial thickness increased in CE/MPA and both CE/BZA groups relative to baseline and relative to placebo.

Table 116: Trial 3115A1-3307: Mean Change From Baseline in Endometrial Thickness

	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
N, pair scans	356	389	183	157	380
Mean (mm)	0.17	0.51	0.09	0.78	0.09
SE	0.08	0.08	0.11	0.12	0.08
Source: CSR 81040, table 10-37					

For Trial 3307, one or more of the criteria for abnormalities of potential clinical importance were met by 23% of subjects overall. Positive endometrial criteria, particularly absolute thickness >8 mm, were most common in subjects assigned to CE/MPA (17%) and CE 0.625/BZA (15%), compared to CE 0.45/BZA (12%), placebo (11%), and BZA 20 mg (8%). Increases in ovarian volume were similar between CE/BZA groups and placebo; detection of ovarian cysts was slightly more frequent with placebo. See Table 117.

Table 117: Trial 3307: Subjects (n, %) with abnormal TVU findings

Trial 3115A1-3307: Subjects with Abnormal TVU Findings					
	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Subjects with scans, N	385	418	195	182	408
Subjects with Potentially Clinically Important Findings					
Total with abnormalities	77 (20)	102 (25)	40 (21)	51 (28)	88 (22)
Endometrial thickness, all	45 (12)	64 (15)	16 (8)	31 (17)	46 (11)
absolute value > 4mm	44 (12)	64 (15)	16 (8)	31 (17)	45 (11)
absolute value > 8mm	3 (<1)	8 (2)	0 (0)	4 (2)	2 (<1)
increase from baseline > 3mm	10 (3)	27 (7)	3 (2)	9 (5)	12 (3)
increase from baseline > 5mm	4 (1)	10 (2)	0 (0)	5 (3)	2 (<1)
Ovarian volume increase from baseline ≥ 2 cm^3	23 (8)	23 (7)	17 (12)	13 (9)	25 (8)
Ovarian cyst visualized	21 (7)	31 (9)	18 (12)	15 (11)	39 (12)
Subjects with Clinically Important Findings					
Endometrial Thickness >8mm	3 (0.8)	9 (2.2)	0	5 (2.8)	2 (0.5)
Ovarian Cyst >20mm	2 (0.4)	5 (1.1)	4 (1.7)	1 (0.5)	2 (0.4)
Source: CSR Tables 10-33, 10-34, 10-36					

In Trial 304, transvaginal ultrasonography was performed at screening and month 12. Mean change in endometrial thickness was not evaluated. Categorical criteria were used to determine potentially clinically important abnormalities. The records for subjects with potentially clinically important abnormalities were then reviewed in a blinded manner to determine those subjects with clinically important findings. The criteria used for determining scans of potential clinical importance were the following:

- endometrial thickness
  - absolute value > 4mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

Table 118 below outlines the categorical criteria for subjects with abnormalities of potential clinical importance in Trial 304. As outlined in the table below, 37 subjects had clinically important endometrial thickness > 8mm. The proportion of subjects with endometrial thickness > 8mm was higher (7%) in the CE 0.625/ BZA 20 group in trial 304 than in Trial 303 (3%) and Trial 3307 (2%). This may be due to the decreased

(b) (4)

Table 118: Subjects with Abnormal TVU Findings

Trial 31151A-304-WW: Subjects with Abnormal TVU Findings				
Test	**BZA 20 / CE0.45 N=361**	**BZA 20/ CE 0.625 N=349**	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Subjects with scans, N	**295**	**291**	**126**	**142**
Subjects with Potentially Clinically Important Findings				
Total with abnormalities	90 (30)	118 (40)	46 (36)	36 (25)
Endometrial thickness, all	59 (20)	93 (32)	34 (27)	19 (13)
absolute value > 4mm	58 (20)	93 (32)	33 (26)	19 (13)
absolute value > 8mm	5 (2)	21 (7)	6 (5)	1 (1)
increase from baseline > 3mm	21 (7)	50 (17)	18 (14)	7 (5)
increase from baseline > 5mm	6 (2)	23 (8)	8 (6)	2 (1)
ovarian volume increase from baseline ≥ 2 cm^3	20 (8)	29 (12)	11 (11)	11 (9)
ovarian cysts visualized	27 (11)	22 (9)	15 (14)	8 (6)
Subjects with Clinically Important Findings				
Endometrial Thickness >8mm	6 (2)	21 (6)	7 (4)	3 (2)
Ovarian Cyst >20mm	4 (1)	1 (<1)	3 (2)	1 (1)
Source: CSR 73414 table 15.92				

Subjects who had TVU findings of endometrial thickness greater than 8 mm or a focal endometrial abnormality were to undergo hysteroscopy and hysteroscopic-directed endometrial biopsy rather than a routine endometrial biopsy. A total of 83 subjects in Trial 303, 14 subjects in Trial 304, and x subjects in Trial 3307 had hysteroscopic-directed endometrial biopsies. These results are discussed in Section 6.4 of this review.

Bone histomorphometry: Bone histomorphometry was not assessed for the conjugated estrogen/bazedoxifene combination product. Anterior iliac crest bone biopsies were obtained from subjects in the bazedoxifene monotherapy trial 301 after 24 months of treatment. A total of 121 subjects underwent bone biopsy. Of these 121 biopsies, 110 were considered evaluable. Qualitative assessment of bone biopsies did not reveal any pathological findings (such as woven bone, bone marrow fibrosis, or osteomalacia) in any of the treatment groups. Quantitative assessments of bone remodeling were performed following two time-spaced courses of tetracycline. Treatment with bazedoxifene resulted in quantitative histomorphometry parameters that were similar for the bazedoxifene and placebo treatment groups. There was no evidence of mineralization defects associated with bazedoxifene therapy.

7.4.6 Immunogenicity

Bazedoxifene and conjugated estrogens are small molecules. Immunogenicity was therefore not formally evaluated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.4.5 and others for uterine hyperplasia issues primarily with the bazedoxifene 10 mg dose.

7.5.2 Time Dependency for Adverse Events

Time dependency was not performed.

7.5.3 Drug-Demographic Interactions

The Applicant examined the effect of age on the incidence of AEs in the 5 Phase 3 BZA/CE studies comparing subjects less than 65 years and subjects 65 years or older. The most commonly reported (≥10% of subjects) AEs in the BZA 20 mg/CE and placebo groups for the less than 65 years subgroup were nasopharyngitis, arthralgia, back pain, pain in extremity, and headache. The most commonly reported AEs among subjects in the greater than 65 years subgroup were abdominal pain, diarrhea, flatulence, fatigue, edema peripheral, influenza, nasopharyngitis, urinary tract infection, arthralgia, back pain, muscle spasm, myalgia, pain in extremity, headache, and hypertension. No clear pattern of treatment group differences was observed.

BZA/CE has not been studied in subjects older than 75 years. Of the total number of subjects in the 5 Phase 3 BZA/CE studies who received BZA/CE, more than 98% were younger than 65, and 1% were older than 65 but none were older than 75 years.

The effect of race (white vs. black vs. other) on AEs was evaluated. As non-white subjects were few, results must be interpreted with caution. Similar trends were noted between subgroups.

The effect of BMI on the incidence of AEs was examined using BMI groups of lower than 25 kg/m^2 and greater than or equal to 25 kg/m^2 at any time on therapy. Little difference was observed among the subgroups.

7.5.4 Drug-Disease Interactions

Studies of CE/BZA in patients with renal and hepatic impairment have not been done. Subjects with impaired hepatic function treated with BZA showed a 4-fold increase in bazedoxifene exposure (Study 112). The Applicant does not recommend use in patients with impaired hepatic function.

7.5.5 Drug-Drug Interactions

No drug interaction studies were conducted with BZA/CE.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The risk of endometrial hyperplasia and carcinoma is increased when estrogens alone are administered alone for prolonged periods. In clinical trials of up to 2 years duration, no increased risk of endometrial cancer was observed in women treated with bazedoxifene/CE.

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. In clinical trials of up to 2 years duration, no increased risk of breast cancer was observed in women treated with bazedoxifene/CE.

In some epidemiological trials, long-term (at least 5-10 years) use of estrogens alone has been associated with an increased risk of ovarian cancer. Other epidemiological trials have not found these associations. In clinical trials of up to 2 years duration, no increased risk of ovarian cancer was observed in women treated with bazedoxifene/CE.

7.6.2 Human Reproduction and Pregnancy Data

BZA/CE has not been evaluated in pregnant or lactating women. No studies were performed on animals to evaluate the effects on reproduction with BZA/CE. The safety of BZA/CE in premenopausal women has not been established.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety of BZA/CE has not been evaluated in a pediatric population, and its use is not recommended.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Per the Applicant, there were no reports of overdose in clinical studies of BZA/CE. There were no reports of drug abuse or other information relevant to the potential for drug abuse in clinical studies of BZA/CE. There were no reports of withdrawal or rebound effects in clinical studies of BZA/CE. In clinical studies of BZA/CE there were no reports of impairment of the senses, coordination, or other factors that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability.

7.7 Additional Submissions / Safety Issues

There was one ongoing trial (B2311014) included in the 120-day safety update which was terminated due to low enrollment. The final report is pending. Preliminary results of the safety analysis showed that 3 adverse events were reported, all of which occurred in the same patient: 2 incidences of somnolence and 1 incidence of arthralgia. Narratives were not provided. Per the sponsor, these events were considered non-serious; they were mild in severity and resolved spontaneously.

8 Postmarket Experience

No postmarketing experience exists for the combination of bazedoxifene/conjugated estrogen. The sponsor submitted postmarket experience for bazedoxifene monotherapy as PSUR 6 and PSUR 7 spanning 1 year duration which was previously submitted to non-US authorities.

Bazedoxifene PSUR 6

PSUR 6 covers the period 17 October 2011 through 16 April 2012 and PSUR 7 covers the period 17 April 2012 through 16 October 2012. Bazedoxifene has received marketing authorization in 35 countries and is currently marketed in 6 countries. Bazeodoxifene 20 mg daily is marketed as Conbriza® in most markets and as Vivant® in others including Japan, Korea, Canada, and Australia, for the treatment and prevention of postmenopausal osteoporosis. During PSUR 6 and PSUR 7 reporting periods, worldwide sales were estimated at (b) (4) standard dosage units (20 mg tablets) of bazedoxifene corresponding to approximately 57,399 patient-years of exposure, and (b) (4) standard dosage units (20 mg tablets) of bazedoxifene corresponding to approximately 86,268 patient-years of exposure, respectively. A total of 207 confirmed cases (37 serious and 170 non-serious) (containing 295 events) in PSUR 6 and a total of 196 cases (65 serious and 131 non-serious) (containing 281 events) in PSUR 7 fulfilled criteria for inclusion.

The most commonly reported adverse events irrespective of the System Organ Class (SOC) for both PSURs were Hot flush, Edema peripheral, Rash/ Rash generalized,

Pruritus/ Pruritus generalized, Visual acuity reduced, Stomatitis, Palpitations, Vision blurred. Additional SOCs reported in only one PSUR were Dizziness, Nausea, Eczema Headache, Chest discomfort, Dyspnea, Hypoaesthesia, Breast discomfort, Weight increased, Constipation, and Drug eruption.

Seven year relative risk rates are as follows: 7 year relative risk of VTE was 1.51 (1 yr RR=2.69, 3 yr RR=1.63 and 5 yr RR of 1.50), visual symptom update, addition of 7 year cardiovascular risk (1.78 for BZA 20 and placebo), 7 year uterine cancer risk (at 7 years, there were no cases of endometrial cancer compared to 7 in the placebo group), and 7 yr breast risk (1.78/1000 woman years BZA vs 1.50/1000 woman-years in placebo).

An overview of sponsor-selected Adverse Events is listed in the Table 1 and 2. These tables exclude cases the sponsor believed not to be relevant. As a result, the numbering of cases in the discussion and in the table do not necessarily correlate. Narratives were not provided in most cases which precluded interpretation by the reviewer.

Table 119: PSUR 6: Selected Adverse Events

Section/Topics	Number of Cases	Comments or Reason(s) for Review[a]
Review of Cases in Current Period		
9.2.1 Venous Thromboembolism	2	1
9.2.2 Ischemic Stroke	2	1
9.2.3 Atrial Fibrillation	1	1
9.2.4 Renal Carcinoma and Adenoma	0	1
9.2.5 New Presentation or Aggravation of Pre-existing Renal Failure or Insufficiency	1	1
9.2.6 Cholecystitis	0	1
9.2.7 Increased Triglyceride Levels	0	1
9.2.8 All Cancers	2	1
9.2.9 Depression	0	1
9.2.10 Ocular Disorders	24	1, 2, 3, 4
9.2.11 Gastroesophageal Reflux Disease	2	1
9.2.12 Ischemic/Thrombotic Cardiac Disorders	1	1
9.2.13 Palpitations and Increased Blood Pressure	5/ 3	4
9.2.14 QT Prolongation	0	4

a. (1) Continued monitoring of the event was indicated in the RMP; (2) the event was considered important from a medical perspective, irrespective of the reporting rate; (3) the event is unlisted/inconsistent with the reference CDS; (4) review or continued monitoring of the event was recommended by a regulatory authority or the MAH in a previous PSUR or other regulatory submission.

Source: PSUR 6, Table 12, p. 27

Table 120: PSUR 7: Selected Adverse Events

Section/Topics	Number of Cases	Comments or Reason(s) for Review[a]
Review of Cases in Current Period		
9.2.1 Venous Thromboembolism	10	1
9.2.2 Ischemic Stroke	1	1
9.2.3 Atrial Fibrillation	0	1
9.2.4 Renal Carcinoma and Adenoma	0	1
9.2.5 New Presentation or Aggravation of Pre-existing Renal Failure or Insufficiency	0	1
9.2.6 Cholecystitis	0	1
9.2.7 Increased Triglyceride Levels	1	1
9.2.8 All Cancers	4	1
9.2.9 Depression	1	1
9.2.10 Ocular Disorders	27	1, 2, 3, 4
9.2.11 Gastroesophageal Reflux Disease	0	1
9.2.12 Ischemic/Thrombotic Cardiac Disorders	1	1
9.2.13 Palpitations: Cumulative Review	20 MC, 0 NMC [b]	4

Section/Topics	Number of Cases	Comments or Reason(s) for Review[a]
9.2.14 Increased Blood Pressure	1	4
9.2.15 QT Prolongation	0	4
9.2.16 Pain in extremity	1	4
9.2.17 Skin and Subcutaneous Tissue Reactions: Cumulative Review	119 MC, 13 NMC[b]	4

a. (1) Continued monitoring of the event was indicated in the RMP; (2) the event was considered important from a medical perspective, irrespective of the reporting rate; (3) the event is unlisted/ inconsistent with the RSI; (4) review or continued monitoring of the event was recommended by a regulatory authority or the MAH in a previous PSUR or other regulatory submission.
b. MC: Medically confirmed. NMC: Non-medically confirmed.

Source: PSUR 7, Table 12, p. 28

Combined PSUR 6 and 7: Tabulation of adverse events of special interest for NDA 22247:

Deaths:
No deaths were reported.

Venous Thromboembolism:
PSUR 6: Two confirmed cases of venous thromboembolism were reported:

(1) 80 year-old female (Case #2011283712) with a lower extremity phlebothrombus. BZA was discontinued and the patient was recovering. No additional details were provided per the sponsor
(2) An 89 year-old female (Case #2011249092) with osteoporosis with report of venous thrombosis of lower extremity after presenting with bilateral lower leg edema 77 days after therapy onset. Positive D-dimer and treated with heparin and warfarin. The event was considered possibly related to BZA

PSUR 7: Twelve cases were reported of venous thromboembolism (VTE) events. Narratives were not provided. Per the sponsor, 2 cases of thrombophlebitis superficial were excluded as they are not considered to be indicative of venous thromboembolism. The remaining 10 cases represent 5.1% of all cases received during the current reporting period, compared with 2 cases (1.0%) during the previous reporting period. The 10 cases reported the following VTE events (of note, 2 cases reported more than 1 VTE event): Pulmonary embolism (3), Deep vein thrombosis (3), Retinal vein thrombosis (2), Thrombosis (2), Retinal vein occlusion (1), and Venous thrombosis limb (1). All 10 cases were assessed as serious. Nine (9) cases involved female patients and gender was unknown in 1 case. Patient age was reported in 9 cases and ranged from 61 to 84 years (mean age of 73.3 years). Case outcome was reported as recovering (3), recovered with sequelae (1), not recovered (3), and unknown (3). There were no cases reporting a fatal outcome. Nine (9) cases originated from Japan and 1 case originated from Spain.

Two ongoing targeted safety studies were ongoing, one of which was a cohort study evaluating venous thromboembolism

Reviewer's comment: The sponsor reports no new safety information was identified. However, the reviewer notes the 5-fold increase in VTE reports across PSURs and believes the increased reporting may signal a greater problem particularly in the older population (mean age 73).

Stroke
PSUR 6: Four cases (1.9%) potentially involving stroke were identified.
(1) The 60-year-old patient (2011283761) experienced cerebral infarction after less than 2 months of bazedoxifene therapy. This patient had no risk factors for cerebral infarction and the only underlying disease was osteoporosis and received concomitant celecoxib.
(2) The 80-year-old patient (2011312911) with a history of hypertension experienced cerebral infarction after receiving bazedoxifene for approximately 4 months and received concomitant celecoxib.
(3) Two cases reported muscular weakness that the sponsor deemed irrelevant. Case histories/narratives were not provided.

PSUR 7: Two cases (1.0%) potentially involving stroke were identified during the current reporting period compared with 4 cases (1.9%) during the previous reporting period. Narratives were not provided. Per the sponsor, 1 case (2012141824) reporting muscular weakness was not relevant. The other case (2012167019) reported a 75-year-old female patient being treated for vertebral with bazedoxifene for 1 month who experienced cerebral infarction. Bazedoxifene was discontinued and the patient recovered with sequelae a month later at the time of the report. The patient also started multiple concomitant medications the same day including celecoxib.

Cardiac Ischemia
PSUR 6: Two cases of cardiac ischemia were reported.
(1) One case (2012077535) described a 62-year-old female patient who experienced myocardial infarction 14 months after starting bazedoxifene therapy for postmenopausal osteoporosis. The medical history for this patient included hypertension and duodenal ulcer; concomitant medications were not reported. Bazedoxifene therapy continued unchanged and the patient recovered.
(2) One case (2011303766) was identified of blood creatinine phosphokinase increased, myalgia, and fatigue. Review of the available information for the case did not suggest cardiac involvement.

PSUR 7: One case (0.5%) involving ischemic/ thrombotic cardiac disorders was identified compared with 0.5% in the previous reporting period. Case 2012133368 involved a 52-year old patient with hypercholesterolemia who was treated with bazedoxifene for approximately 7 months and experienced a transient ischemic attack for which she was hospitalized. Results of a head CT scan, an EEG, and an abdominal

ultrasound were normal. Bazedoxifene was discontinued and the outcome was unknown.

Malignancy

PSUR 6: One case report of ovarian neoplasm progression was identified. In this serious case (2012017370), a 61-year-old female patient with a medical history of ongoing ovarian neoplasm was found to have an ovarian cystoma enlargement approximately one month after initiating treatment with bazedoxifene; therapy continued unchanged.

PSUR 7: There were 4 cases of cancer (2%) identified during the current reporting period, compared with 1 case (0.5%) during the previous reporting period. These cases reported the events: breast cancer recurrent (2), breast cancer (1), and metastases to bone (1). Narratives were not provided.

Two (2) cases contained limited information. Case 2012246847 reported metastases to bone in a patient who started bazedoxifene and had a medical history of breast cancer. No additional information was provided. A second case, 2012238238, provided no details regarding medical history, concomitant medications, and duration of bazedoxifene therapy in relation to the event onset. Bazedoxifene was discontinued and the patient was recovering at the time of the report after receiving treatment with anastrozole.

In the two recurrent breast cancer cases (2012239447 and 2012243097), the first patient reportedly had not started tamoxifen yet. The second case described that the patient had
experienced previous recurrences requiring surgeries for breast cancer.

When all cancers were accessed, the BZA rate was 5.2% vs 4.2% for placebo. No imbalances were seen at 7 years.

Reviewer's comment: The sponsor reports no new safety information was identified. However, the reviewer notes the 4-fold increase in breast cancers but with 2 cases representing recurrence of malignancy. Due to the few reports, it does not appear that this represents a change in the safety risk.

Breast Disorders

PSUR 6: One event each of breast discomfort, breast disorder, breast enlargement was reported.

PSUR 7: Breast discomfort was reported in 5 cases and was considered non-serious in all. Patient age was reported in 4 cases and ranged from 55 to 70 years of age with a mean age of 62.3 years. Event outcome was reported as resolved in 1 case and was unknown in 4 cases. All 5 cases described breast discomfort as "breast tension." Two

cases either co-reported breast enlargement and weight increased (2012252134) or described an increase in bra size (2012203677). One case (2012149053) indicated possible association with sulpiride. The 2 remaining cases contained limited information for a clinical assessment and lacked information regarding patient medical history and concomitant medication. Case 2012110350 described the patient's breast discomfort resolved after discontinuing bazedoxifene. Case 2012137447 was assessed as probable causal association with bazedoxifene in a patient who continued therapy; the event outcome was unknown.

Uterine Disorders
PSUR 6: One case each of uterine hemorrhage and vaginal hemorrhage were reported. Two cases of menorrhagia were reported. One case of endometrial hypertrophy was reported. Individual narratives were not provided.

PSUR 7: Uterine hemorrhage (1), endometrial hypertrophy (1) and metorrhagia (2) were reported.

Fracture
PSUR 6: No events were reported.
PSUR 7: Three events were reported (fall, femoral neck fracture and upper limb fracture).

Other Events

Ocular Events:
PSUR 6: A total of 24 ocular events were reported with 17/24 considered serious. Twenty-two (22) of the 24 cases originated from Japan, with the remaining 2 cases originating from Spain. Patient ages, reported in 21 cases, ranged from 60 to 82 years; mean age was 71.5 years. Seventeen (17) patients were elderly (≥65 years of age). Outcomes for the 24 cases were reported as recovered in 9 cases, recovering in 4 cases, not recovered at the time of the report in one case, and unknown in 10 cases. Most often, resolution of the events was associated with discontinuation of bazedoxifene therapy. In 17 of the 24 cases, bazedoxifene therapy was discontinued permanently or temporarily; patients recovered or were recovering at the time of the report in 12 of these 17 cases. A tabulation of events is listed in Sponsor Table 121 below. Visual acuity reduced, Vision blurred and visual impairment was reported in 15 out of 32 cases (47%).

Table 121: PSUR 6: Ocular Adverse Events

Preferred Term	Total AEs	Non-Serious AEs	Serious AEs
Visual acuity reduced	7	0	7
Vision blurred	5	0	5
Visual impairment	3	0	3
Dry eye	2	2	0
Abnormal sensation in eye	1	1	0
Astigmatism	1	1	0
Cataract	1	0	1
Diplopia	1	1	0
Erythema of eyelid	1	1	0
Eye haemorrhage	1	0	1
Eyelid disorder	1	1	0
Eyelid ptosis	1	0	1
Lacrimation increased	1	1	0
Myopia	1	1	0
Ocular hyperaemia	1	1	0
Oculogyric crisis	1	0	1
Photophobia	1	0	1
Photopsia	1	0	1
Vitreous floaters	1	1	0
Total Ocular AEs[a]	**32**	**11**	**21**

[a]A case may include more than one event.

Source: Table 13, PSUR6, p. 31

PSUR 7:A total of 27 (13.8%) medically confirmed cases involving ocular disorders were received, compared to 11.6% (24 cases) of all cases reported ocular disorders. All 27 cases for the current reporting period were from spontaneous sources of which 24
were considered serious and 3 were non-serious. Twenty-five (25) of the 27 cases originated from Japan, with the remaining 2 cases originating from Spain. Patient ages, reported in 23 cases, ranged from 31 to 85 years; mean age was 67.7 years. Seventeen (17) patients were elderly (≥65 years of age). Outcomes for the 27 cases were reported as recovered in 8 cases, recovering in 1 case, not recovered at the time of the report in 6 cases, and unknown in 12 cases.

The ocular adverse events are located in Table 122.

Table 122: PSUR 7: Ocular Adverse Events

Preferred Term	Total AEs	Non-Serious AEs	Serious AEs
Vision blurred [b]	11	0	11
Visual acuity reduced [b]	7	0	7
Eye pain [b]	2	1	1
Ocular hyperaemia	2	2	0
Retinal vein thrombosis [b]	2	0	2
Abnormal sensation in eye	1	1	0
Lacrimation increased	1	1	0
Optic neuritis	1	0	1
Photopsia [b]	1	0	1
Retinal vein occlusion	1	0	1
Sudden visual loss	1	0	1
Visual impairment [b]	1	0	1
Total Ocular AEs [a]	**31**	**5**	**26**

[a] A case may include more than one event.
[b] Event listed in the RSI.

Source: PSUR7, Table 13, p. 35

Reviewer conclusion: A 5-fold increase in VTEs was reported in PSUR 7 compared to PSUR 6. Prior PSURs are not available to the reviewer. This increase may suggest an important signal particularly in the older population (mean age 73). Non-specific ocular events were prominent in both PSURs and do not appear to be related to venous thrombembolism. The applicability of these data to the combination product is unknown.

9 Appendices

9.1 Literature Review/References

Current Estrogen and Progestin FDA Guidance:

Draft Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation (2003)

Women's Health Initiative (WHI) References:

Estrogen-Alone Studies:

Curb et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus, Arch Intern Med. 2006;166(7):772-780.

Hsia et al. Conjugated Equine Estrogens and Coronary Heart Disease, Arch Intern Med. 2006;166(3):357-365

Shumaker et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women, JAMA. 2004;291(24):2947-2958.

The Women's Health Initiative Steering Committee. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy, JAMA. 2004;291(14):1701-1712.

Estrogen-plus-Progestin Studies:

Cushman et al. Estrogen Plus Progestin and Risk of Venous Thrombosis, JAMA. 2004;292(13):1573-1580.

Manson et al. Estrogen plus Progestin and the Risk of Coronary Heart Disease, N Engl J Med 2003;349:523-34.

Shumaker et al. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women, JAMA. 2003;289(20):2651-2662.

Wassertheil-Smoller et al. Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women, JAMA. 2003;289(20):2673-2684.

Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, JAMA. 2002;288(3):321-333.

Prior NDA Reviews

(b) (4)

(b) (4)

9.2 Labeling Recommendations

Labeling negotiations are ongoing. The clinical reviewer recommends the following:

- All references to the product should be in conjugated estrogens/bazedoxifene format.
- The approved indications should include "in women with a uterus". See final approved labeling.
- Limiting use in patients aged > 75 years should be considered.
- Use is not recommended in patients with hepatic impairment.
- (b) (4)
- Clinical data from estrogen product labeling based on the WHI should be carefully evaluated for inclusion in CE/BZA labeling.

9.3 Advisory Committee Meeting

An Advisory Committee was not convened for this application.

9.4 Tables of Approved Drugs for the Proposed Indications

Table 123: Approved Products for Treatment of Vasomotor Symptoms

Oral Estrogen-Alone Products	**Available Dosage Strengths**
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
Cenestin® (synthetic conjugated estrogens, A)	0.625 mg, 0.9 mg, or 1.25 mg once daily
Enjuvia® (synthetic conjugated estrogens, B)	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Menest® (esterified estrogens)*	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Estrace® (estradiol)	0.5 mg, 1.0 mg, or 2.0 mg once daily
Femtrace® (estradiol acetate)	0.45 mg, 0.9 mg, or 1.8 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Transdermal Products	**Available Dosage Strengths**
Alora® (estradiol matrix patch)	0.025 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Climara® (estradiol matrix patch)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied once weekly
Esclim® (estradiol matrix patch)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly

Transdermal Products, cont	**Available Dosage Strengths**
Vivelle® (estradiol matrix patch)	0.05 mg/day or 0.1 mg/day; patch applied twice weekly
VivelleDot® (estradiol matrix patch)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Various Generics (estradiol matrix patch)	0.05 mg/day or 0.1 mg/day; patch applied once or twice weekly
Estraderm® (estradiol reservoir patch)	0.05 mg/day or 0.1 mg/day; patch applied twice weekly
Minivelle (estradiol)	0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg once daily
Topical Products	**Available Dosage Strengths**
EstroGel® 0.06% (estradiol gel)	0.075 mg/day; 1.25 gram applied once daily
Elestrin® (estradiol gel)	0.52 mg/day or 1.04 mg/day; 0.87 gram or 1.7 gram applied once daily
Divigel (estradiol gel) 0.1%	0.25 mg/day, 0.5 mg/day, or 1.0 mg/day; 0.25 gram, 0.5 gram or 1.0 gram applied once daily
Estrasorb® (estradiol topical emulsion)	0.05 mg/day; two 1.74 gram pouch applied once daily
Evamist® (estradiol transdermal spray)	1, 2 or 3 spray(s) 90 mcL containing 1.53 mg estradiol applied once daily
Vaginal Cream	**Available Dosage Strengths**
Premarin® (conjugated estrogens) Vaginal Cream	0.5 to 2 grams (0.625 mg per gram) inserted intravaginal daily
Estrace (estradiol) Vaginal Cream	2 to 4 grams (0.1 mg per gram) inserted intravaginal daily for 1 to 2 weeks, then 1 gram inserted intravaginal daily thereafter
Vaginal Rings	**Available Dosage Strengths**
Estring® (estradiol)	Release of 7.5 mcg estradiol/day; ring worn for 90 days
Femring® (estradiol acetate)	Release of 0.05 mg estradiol/day or 0.10 mg estradiol/day; ring worn for 90 days
Vaginal Tablet	**Available Dosage Strengths**
Vagifem® (estradiol hemihydrate)	10 mcg/day or 25 mcg/day; vaginal tablet inserted twice weekly
Oral Estrogen Plus Progestin Products	**Available Dosage Strengths**
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE/day plus 1.5 mg MPA/day taken daily or 0.625 mg CE/day plus 2.5 mg or 5.0 mg MPA/day taken daily
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE/day taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA/day taken daily on days 15-18
femhrt® (ethinyl estradiol [EE] plus norethindrone acetate [NETA])	2.5 mcg EE/day plus 0.5 mg NETA/day taken daily or 5 mcg EE/day plus 1.0 mg NETA/day taken daily
Activella® (estradiol [E2] plus norethindrone acetate [NETA])	0.5 mg E2/day plus 0.1 mg NETA/day taken daily or 1 mg E2/day plus 0.5 mg NETA/day taken daily
Angeliq® (estradiol [E2] plus drospirenone)	1 mg E2/day plus 0.5 mg drospirenone/day taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2/day taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate/day taken daily for 3 days, repeated continuously

Transdermal Estrogen Plus Progestin Products	Available Dosage Strengths
CombiPatch (estradiol [E2] plus norethindrone Acetate [NETA])	0.05 mg E2/day plus 0.14 mg NETA/day; patch applied twice weekly 0.05 mg E2/day plus 0.25 mg NETA/day; patch applied twice weekly
ClimaraPro® (estradiol [E2] plus levonorgestrel)	0.05 mg E2/day plus 0.015 mg levonorgestrel/day; patch applied once weekly

Table 124: Approved Products for Treatment of Vulvar and Vaginal Atrophy

Oral Estrogen-Alone Products	Available Dosage Strengths
Cenestin® (synthetic conjugated estrogens, A)	0.3 mg once daily
Enjuvia® (synthetic conjugated estrogens, B)	0.3 mg once daily
Estrace® (estradiol)	0.5 mg, 1.0 mg, or 2.0 mg once daily
Menest® (esterified estrogens)*	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
Transdermal Products	**Available Dosage Strengths**
Alora® (estradiol transdermal system)	0.025 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Climara® (estradiol transdermal system)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied once weekly
Esclim® (estradiol transdermal system)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Estraderm® (estradiol transdermal system)	0.05 mg/day or 0.1 mg/day; patch applied twice weekly
VivelleDot® (estradiol transdermal system)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Various Generics (estradiol transdermal system)	0.05 mg/day or 0.1 mg/day; patch applied once or twice weekly
Topical Products	**Available Dosage Strengths**
EstroGel® 0.06% (estradiol gel)	0.075 mg/day; 1.25 gram applied once daily
Vaginal Cream	**Available Dosage Strengths**
Estrace (estradiol) Vaginal Cream	2 to 4 grams (0.1 mg per gram) inserted intravaginal daily for 1 to 2 weeks, then 1 gram inserted intravaginal daily thereafter
Premarin® (conjugated estrogens) Vaginal Cream	0.5 to 2 grams (0.625 mg per gram) inserted intravaginal daily
Vaginal Rings	**Available Dosage Strengths**
Estring® (estradiol)	Release of 7.5 mcg estradiol/day; ring worn for 90 days
Femring® (estradiol acetate)	Release of 0.05 mg estradiol/day or 0.10 mg estradiol/day; ring worn for 90 days
Vaginal Tablet	**Available Dosage Strengths**
Vagifem® (estradiol hemihydrate)	10 mcg/day or 25 mcg/day; vaginal tablet inserted twice weekly
Oral Estrogen Plus Progestin Products	**Available Dosage Strengths**
Angeliq® (estradiol [E2] plus drospirenone)	1 mg E2/day plus 0.5 mg drospirenone/day taken daily

Oral Estrogen Plus Progestin Products, cont	**Available Dosage Strengths**
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2/day taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate/day taken daily for 3
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE/day taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA/day taken daily on
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE/day plus 1.5 mg MPA/day taken daily or
Transdermal Estrogen Plus Progestin Products	**Available Dosage Strengths**
CombiPatch® (estradiol [E2] plus norethindrone Acetate [NETA])	0.05 mg E2/day plus 0.14 mg NETA/day; patch applied twice weekly
Estrogen Agonist/Antagonist	**Available Dosage Strengths**
Osphena®	60mg daily po

Table 125: Approved Products for Prevention of Postmenopausal Osteoporosis

Bisphosphonates	**Available Dosage Strengths**
Fosamax® (alendronate)	5 mg daily, 35 mg weekly po
Actonel® (risedronate)	5 mg daily, 35 mg weekly po
Actonel with Calcium® (risedronate)	35 mg once weekly,1250 mg days 2-7 po
Boniva® (ibandronate)	2.5 mg daily,150 mg monthly po
Reclast® (zoledronic acid)	5 mg IV every 2 years
Estrogen Agonist/Antagonist	**Available Dosage Strengths**
Evista® (raloxifene)	60 mg daily po
Calcitonin	**Available Dosage Strengths**
Miacalcin® (salmon calcitonin, synthetic)	100 IU SQ every other day
Miacalcin® (salmon calcitonin, synthetic)	200 IU daily NS
Fortical® (salmon calitonin, recombinant)	200 IU daily NS
Estrogen and Estrogen combination products	**Available Dosage Strengths**
Premarin® (conjugated estrogen)	0.3 – 1.25 mg daily po
Premphase® (Conjugated estrogen, medroxyprogesterone acetate)	0.625 mg daily D1-14 5 mg D 15-28 po
Prempro® (Conjugated estrogen, medroxyprogesterone acetate)	0.3/1.5 to 0.625/5 mg daily po
Climara® (estradiol)	0.025 – 0.1 mg/day, applied once weekly TD
Climara Pro® (estradiol, levonorgestrel)	0.45/0.015 mg/day, applied once weekly po TD
Prefest® (estradiol, norgestimate	1 mg estradiol daily for 3 days; alternate with 1/0.09 mg daily for 3 days po
Femhrt®	2.5/0.5 – 5/1 mg daily po
Activella® (estradiol, norethindrone acetate)	0.5/0.1– 1/0.5 daily po
Vivelle® (estradiol)	0.025 – 0.1 mg/day, applied twice weekly TD
Alora® (estradiol)	0.025 – 0.1 mg/day, applied twice weekly TD
Menostar® (estradiol)	0.014 mg/day, applied once weekly TD
Vivelle Dot® (estradiol)	0.025 – 0.1 mg/day, applied twice weekly TD

9.5 Clinical Investigor Finanacial Disclosure Form

Clinical Investigator Financial Disclosure

Application Number: NDA 22247

Submission Date(s): September 26, 2012 (submitted), October 3, 2012 (received)

Applicant: Wyeth

Product: Conjugated estrogen/bazedoxifene

Reviewers: Marcea Whitaker, M.D., Steve Bienz, M.D., Gerald Willett, M.D., Stephen Voss, M.D., Theresa Kehoe, M.D.

Date of Review: June 5, 2013

Covered Clinical Studies: There were a total of 13 covered studies included in the NDA application (See Table 126 and **Error! Reference source not found.**). The sponsor included the financial disclosure information for bazedoxifene monotherapy and bazedoxifene/conjugated estrogen in the application. The approval of this NDA does not rely on data from bazedoxifene monotherapy and therefore, some responses are limited to investigators involved in the bazedoxifene/conjugated estrogen combination program (Studies 203, 303, 305, 306, 3307 and 304) and are designated by an asterisk (*).

Table 126: List of Covered Studies

#	Study #	Title	LSLVD
	Covered Studies under Legacy Wyeth		
1	B178:3068A1-200	A double-blind, randomized, controlled study of the effects of TSE-424 on biochemical markers of bone metabolism in healthy postmenopausal women	21 Feb 2001
2	B178:3068A1-203*	A multicenter, double-blind, randomized, controlled, pilot trial of the combination of premarin with TSE-424 on the estrogenic stimulation of the endometrium in healthy postmenopausal women	07 Mar 2000
3	B178:3068A1-204	A multicenter, double-blind, randomized, active- and placebo-controlled pilot trial of the vasomotor effect of TSE-424 in nonflushing, postmenopausal women	26 Apr 2000
4	B178:3068A1-300	A multicenter, double-blind, randomized, placebo and Raloxifene controlled study to assess safety and efficacy of TSE-424 (Bazedoxifene Acetate) in the prevention of postmenopausal osteoporosis	12 Jul 2004
5	B178:3068A1-303	A multicenter, double blind, randomized, placebo controlled study to assess the safety and efficacy of Bazedoxifene in postmenopausal Asian women	08 Sep 2007
6	B231:3115A1-303*	A double-blind, randomized, placebo- and active-controlled safety and efficacy study of Bazedoxifene/Conjugated Estrogens combinations in postmenopausal women	13 Jan 2006
7	B231:3115A1-304*	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	02 Sep 2008
8	B231:3115A1-305*	A double-blind, randomized, placebo-controlled,	06 Feb 2007

#	Study #	Title	LSLVD
	Covered Studies under Legacy Wyeth		
		efficacy and safety study of Bazedoxifene/Conjugated Estrogen combinations for treatment of vasomotor symptoms associated with menopause	
9	B231:3115A1-306*	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	12 Mar 2007

#	Study #	Title	DBLD
	Covered Studies under Pfizer		
1	B178:3068A1-301	Fracture incidence reduction and safety of TSE-424 (Bazedoxifene Acetate) compared to placebo and Raloxifene in osteoporotic postmenopausal women	18 Feb 2011
2	B178:3068A1-400	Evaluation of changes in mammographic breast density associated with Bazedoxifene, Raloxifene, and placebo in postmenopausal women: an ancillary study of Protocol 3068A1-301-WW	24 Oct 2007
3	B231:3115A1-3307*	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	05 Mar 2011
4	B231:3115A1-4000*	Evaluation of changes in mammographic breast density associated with Bazedoxifene Acetate/Conjugated Estrogens, Raloxifene and placebo in postmenopausal women: an ancillary study of Protocol 3115A1-303-WW	23 Aug 2010

* BZA/CE clinical program
LSLV = last subject last visit date
DBLD = database lock date
Source: Financial disclosure summary; page 2 of 462

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 215		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None. (There were no full time employees.) However, 34* investigators were on the speaker's bureau and/or received honoraria		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 105		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None. However 54* investigators received other payments (i.e., honoraria) (See Table 127) Significant payments of other sorts: 2* Proprietary interest in the product tested held by investigator: 0* Significant equity interest held by investigator in sponsor of covered study: 2*		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 66*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

* Report limited to Studies 203, 303, 305, 306, 3307, and 304

Reviewer's comments:

- **The Applicant has adequately disclosed the financial interests/arrangements of the investigators and appears to have demonstrated due diligence in obtaining missing data. The financial disclosure amounts for studies evaluating the combination of bazedoxifene and conjugated estrogen range from $26,000 to $626,000. These amounts are much higher than what is generally seen in NDAs submitted to the Agency. The majority of the investigators with disclosed financial interests in excess of $25,000** (b) (6)

(b) (6)

The sponsor states "the investigators were not involved in the analyses of these studies and/or efficacy data obtained from the patients and are not anticipated to benefit directly from the sale of the drug product." In this reviewer's opinion, based on the amount financial compensation, it is reasonable to assume some bias may have occurred and the data may have been compromised intentionally or unintentionally at the patient level. However, since the main endpoints, endometrial biopsies and bone mineral density, were read centrally and vasomotor symptom data were recorded on patient diary cards, the results were objective and the individual effect on the subject level data is anticipated to be small. In addition, for most of the larger financial disclosure amounts, the investigator accounted for (b) (6) the enrolled population (b) (6)

- **Based on the information above, the financial disclosure information appears not to affect the approvability of the application.**

- **At this time it is unclear if these financial disclosures included the central radiologists. Clarification from the sponsor has been requested.**

Table 127: Significant Financial Payment to Investigators

Protocol number	Investigator	Center	[1]Subjects Enrolled at Site n (%)	Total amount (USD) Or Stock Holding
(b) (6)				
				26,315.72
				306,105.72
				Stock (Pfizer) Est $368,000
				30,500.00
				Stock (Pfizer) Est. $117,000
				26,315.72
				306,105.72
				160,467.25
				625,689.76
				61,632.81
				46,426.67
				207,297.88
				62,868.01
				75,388.03
				91,832.13

Protocol number	Investigator	Center	[1]Subjects Enrolled at Site n (%)	Total amount (USD) Or Stock Holding
(b) (6)				104,861.90
				29,374.51
				556,142.99
				52,896.10
				47,823.32
				72,051.40
				47,563.23
				256,569.60
				29,944.24
				34,005.83
				46,261.25
				214,789.11
				61,719.58
				84,519.52
				65,118.73
				100,311.25
				86,604.02
				625,689.76
				62,868.01
				75,388.03
				37,473.74
				77,544.46
				46,261.25
				100,311.25
				31,863.95
				34,876.22
				46,261.25
				65,118.73
				306,105.72
				160,467.25
				86,604.02
				30,816.70
				46,426.67
				44,709.04
				91,832.13
				556,142.99
				52,896.10
				40,642.68
				34,281.72
				52,369.92
				61,719.58
				84,519.52
(b) (6)				

Protocol number	Investigator	Center	[1]Subjects Enrolled at Site n (%)	Total amount (USD) Or Stock Holding
(b) (6)				

9.6 Safety Evaluation – Individual Trials

Trial 303

Protocol 3115A1-303-US/EU/BR (Study 303): A double-blind, randomized, placebo- and active-controlled safety and efficacy study of bazedoxifene/conjugated estrogens combinations in postmenopausal women.

Adverse Event Rates

Safety event rates for Trial 303 are shown in Table 128. Treatment emergent adverse events occurred in similar percentages of subjects across treatment groups, with from 90 to 94% of subjects in each active treatment group and 92% in placebo reporting at least one adverse event. No more than one death occurred per treatment group. Serious adverse events were evenly distributed, with 6 to 8% of subjects in each active treatment group reporting SAEs compared to 8% in placebo. The percentage of subjects withdrawn for AEs was also evenly balanced across treatment groups, ranging from 11 to 16% (15% in placebo). The number of subjects who withdrew for other reasons than adverse event but had an ongoing treatment emergent adverse event ranged from 8 to 15% per treatment group. When the percentage of subjects withdrawing for AE and the percentage of subjects withdrawing for other reasons but with an ongoing treatment emergent adverse event were summed, the results ranged from 23 to 27% in each active treatment group and 28% for placebo.

Table 128: Safety Event Rates for Trial 303

Event	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Any TEAE	405(94)	384(93)	387(93)	400(93)	404(93)	382(90)	393(93)	394(92)	0.607
Deaths	1 (<1)	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)[2]	1 (<1)	
SAE	32 (7)	23 (6)	24 (6)	35 (8)	26 (6)	26 (6)	32 (8)	34 (8)	0.633
WD for AE	67 (16)	53 (13)	50 (12)	63 (15)	47 (11)	46 (11)	60 (14)	62 (15)	0.283
Other WD with TEAE	36 (8)	51 (12)	59 (14)	39 (9)	54 (12)	62 (15)	53 (13)	54 (13)	

Source: Clinical Study Report 64104, Tables 10-2 and 10-4 and datasets
1 P-value for Chi-square
2 Death occurred more than 15 days after study completion

Exposure

The number and percent of subjects reaching specified durations of treatment are shown in Table 129. A total of 3397 subjects were randomized and took at least one

dose of study drug and are included in safety evaluations. From 64 to 69% of subjects completed two years of the study in the active treatment groups compared to 64% in placebo.

Table 129: Trial 303 Duration of Treatment

Duration	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
> 6 weeks	413 (96)	397 (96)	396 (95)	415 (97)	414 (96)	397 (94)	400 (95)	406 (95)
> 12 weeks	406 (94)	386 (93)	385 (92)	403 (94)	404 (93)	389 (92)	385 (91)	393 (92)
> 6 months	382 (89)	362 (87)	359 (86)	370 (86)	377 (87)	358 (85)	353 (83)	364 (85)
> 1 year	332 (77)	319 (77)	316 (76)	333 (77)	337 (78)	316 (75)	298 (70)	313 (73)
> 18 months	307 (71)	298 (72)	296 (71)	308 (72)	318 (73)	294 (70)	287 (68)	289 (68)
2 years	291 (68)	282 (68)	277 (66)	285 (66)	297 (69)	278 (66)	269 (64)	275 (64)
Source: Clinical Study Report 64104, Tables 10-1								

Compliance, defined as taking at least 80% of scheduled study drug, was calculated for each study week through Week 12, and then for each 4-week period through week 104. At least 90% of subjects in each treatment group were compliant in each period.

Deaths

There were 5 deaths in the trail during therapy and the 15 day follow-up period. A sixth death was reported more than 15 days after withdrawal from the trial (raloxifene).

BZA 10 mg/CE 0.625 mg:

- A 59 year old woman with a long smoking history discontinued study medicine on Day 494 and died on Day 515 due to intracerebral hemorrhage secondary to metastatic lung cancer

BZA 20 mg/CE 0.625 mg:

- A 56 year old woman died on Day 631 as a result of a motor vehicle accident

BZA 40 mg/CE 0.625 mg:

- A 52 year old obese woman with hypertension died on Day 642 in her sleep as a result of aspiration. The family refused to provide information beyond the death certificate

BZA 10 mg/CE 0.45 mg:

- None

BZA 20 mg/CE 0.45 mg:

- None

BZA 40 mg/CE 0.45 mg:

- A 52 year old woman died on Day 183 as a result of a small airplane accident

Raloxifene:

- A 57 year old woman withdrew from the trial on Day 181 and died about Day 270. Pulmonary nodules were known to have been present, but cause of death is unknown.

Placebo:

- A 53 year old woman with a long smoking history died on Day 342 of an acute exacerbation of COPD

Reviewer's comment: No concerning pattern of deaths is noted. The deaths from aspiration during sleep (BZA 40 mg/CE 0.625 mg), associated with pulmonary nodules (raloxifene), and exacerbation of COPD (placebo) could potentially be from pulmonary embolism, but with few suspicious factors noted that concern is not high.

Serious Adverse Events

Serious adverse events reported on therapy and to 15 days post therapy in Trial 303 are shown in Table 130, where at least two subjects in a treatment group reported that SAE for the system organ class or preferred term. As SAEs reported during screening are not included, totals differ slightly from Table 1.

In general, SAEs are present in small numbers, are balanced between treatment groups, and are not markedly higher than placebo or the active raloxifene comparator. From 6 to 8% of subjects in each active treatment group reported a SAE compared to 7% in placebo.

Neoplasms Benign, Malignant, and Unspecified represented the SOC with the most reported SAEs. All cancers were to be reported as SAEs. Overall, neoplasms reported as SAEs were balanced with 11 subjects (3%) in the BZA 10 mg/CE 0.45 mg group, 4 to 7 subjects (1-2%) in other BZA/CE groups, 8 subjects (2%) in the raloxifene group, and 7 subjects (2%) on placebo. The most common preferred term reported was basal cell carcinoma by 1 to 3 subjects (<1-1%) in the BZA/CE groups, 2 subjects (<1%) in the raloxifene group, and 3 subjects (1%) on placebo. The next most common preferred terms were combined squamous cell carcinoma (all of the skin) by 0 to 2 subjects (0-<1%) in the BZA/CE groups, 2 subjects (<1%) in the raloxifene group, and 2 subjects (<1%) on placebo. See the discussion of malignancies under Adverse Events of Special Interest below.

An imbalance of SAEs was noted in the SOC cardiac disorders, with more subjects in the CE 0.625 mg treatment groups reporting SAEs (4 subjects (1%) in the BZA 10 mg/CE 0.625 mg group, 3 subjects (1%) in the BZA 20 mg/CE 0.625 mg group, and 3 subjects (1%) in the BZA 40 mg/CE 0.625 mg group; no more than 1 subject in any other group). In the BZA 10 mg/CE 0.625 mg group, all 4 subjects reported coronary artery disease. In the BZA 20 mg/CE 0.625 mg group, one subject reported CAD and 1 reported myocardial infarction. Women's Health Initiative Studies showed increased risk of non-fatal myocardial infarction with estrogen plus progesterone but not with estrogen alone. This finding in the current study will need to be further compared with the other clinical studies. Raloxifene was associated with an increased risk of chest pain (5 subjects (1%), no more than one subject in any other group).

The BZA 10 mg/CE 0.45 mg group had an unexplained increased incidence of SAEs of pneumonia (5 subjects (1%), no more than one subject in any other active treatment group and 2 subjects in placebo). This is likely a chance occurrence.

Fractures reported as SAEs were balanced across treatment groups except 4 subjects (1%) were reported in the raloxifene group with 2 subjects (<1%) in placebo and one (<1%) in each of the BZA/CE groups. See the discussion of fractures under Adverse Events of Special Interest below.

All preferred terms for CVAs and TIAs within the Nervous System Disorders SOC were combined as numbers for individual preferred terms were small. All CVA and TIA PTs combined reported as SAEs may be more common in the BZA/CE groups (3 subjects (1%) in the BZA 10 mg/CE 0.625 mg group, no subjects in the BZA 20 mg/CE 0.625 mg group, 2 subjects (<1%) in the BZA 40 mg/CE 0.625 mg group, 1 subject (<1%) in the BZA 10 mg/CE 0.45 mg group, 1 subject (<1%) in the BZA 20 mg/CE 0.45 mg group, and 1 subject (<1%) in the BZA 40 mg/CE 0.45 mg group, no subjects with either raloxifene or placebo). This finding will need to be further compared with the other clinical studies. Cerebrovascular events have been a concern both with estrogens and bazedoxifene monotherapy.

There were 3 reported SAEs of endometrial hyperplasia in the BZA 10 mg/CE 0.625 mg group, but the only other case was in placebo. This finding is concerning for lack of endometrial protection with the 10 mg BZA dose.

Table 130: Trial 303 Serious Adverse Events Reported on- or Post-Therapy, at least 2 Subjects in a Treatment Group

SOC PT[1]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Any SAE	30 (7)	23 (6)	24 (6)	35 (8)	24 (6)	25 (6)	31 (7)	30 (7)
Blood & lymph	1 (<1)	0	0	0	2 (<1)	0	0	1 (<1)
Anemia	1 (<1)	0	0	0	2 (<1)	0	0	0
Cardiac	4 (1)	3 (1)	3 (1)	1 (<1)	0	1 (<1)	0	1 (<1)
CAD	4 (1)	1 (<1)	1 (<1)	0	0	0	0	0
Eye	0	0	1 (<1)	0	1 (<1)	0	0	2 (<1)
Cataract	0	0	0	0	0	0	0	2 (<1)
GI	5 (1)	2 (<1)	2 (<1)	1 (<1)	2 (<1)	5 (1)	2 (<1)	2 (<1)
Gen & ad site	1 (<1)	2 (<1)	1 (<1)	3 (1)	2 (<1)	2 (<1)	7 (2)	2 (<1)
Chest pain	0	1 (<1)	0	1 (<1)	1 (<1)	0	5 (1)	0
Hepatobiliary	4 (1)	0	1 (<1)	2 (<1)	3 (1)	4 (1)	2 (<1)	1 (<1)
Cholecystitis	2 (<1)	0	0	0	1 (<1)	2 (<1)	1 (<1)	0
Cholelithiasis	1 (<1)	0	1 (<1)	1 (<1)	3 (1)	2 (<1)	1 (<1)	1 (<1)
Infections & inf	2 (<1)	4 (1)	4 (1)	8 (2)	2 (<1)	0	3 (1)	4 (1)
Appendicitis	0	0	1 (<1)	2 (<1)	0	0	0	0
Pneumonia	0	1 (<1)	0	5 (1)	1 (<1)	0	1 (<1)	2 (<1)
Injury, poison	3 (1)	2 (<1)	4 (1)	3 (1)	2 (<1)	1 (<1)	4 (1)	2 (<1)

SOC PT[1]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Fall	0	0	2 (<1)	0	0	0	0	0
Fracture (all)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	4 (1)	2 (<1)
Investigations	0	0	0	2 (<1)	0	1 (<1)	2 (<1)	3 (1)
ALT increased	0	0	0	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)
AST increased	0	0	0	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)
Metab & nutrit	0	0	1 (<1)	0	1 (<1)	0	0	2 (<1)
Dehydration	0	0	1 (<1)	0	1 (<1)	0	0	2 (<1)
MS and CT	1 (<1)	3 (1)	2 (<1)	3 (1)	1 (<1)	1 (<1)	4 (1)	3 (1)
Osteoarthritis	1 (<1)	0	0	0	0	0	2 (<1)	0
Neoplasms	4 (1)	4 (1)	4 (1)	11 (3)	7 (2)	5 (1)	8 (2)	7 (2)
Basal cell ca	3 (1)	2 (<1)	1 (<1)	3 (1)	1 (<1)	1 (<1)	2 (<1)	3 (1)
Breast ca (all)	0	0	1 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)
Sq cell ca (all)[2]	0	0	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	2 (<1)
Ut leiomyoma	0	0	0	0	2 (<1)	0	1 (<1)	0
Nervous system	6 (1)	1 (<1)	3 (1)	2 (<1)	4 (1)	2 (<1)	1 (<1)	2 (<1)
CVA/TIA (all)	3 (1)	0	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0
Dizziness	2 (<1)	0	0	1 (<1)	0	0	0	0
Hypoesthesia	0	0	1 (<1)	0	2 (<1)	1 (<1)	1 (<1)	0
Psychiatric	0	0	0	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0
Bipolar	0	0	0	0	2 (<1)	0	0	0
Renal & urinary	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)	1 (<1)	1 (<1)
Repro & breast	4 (1)	0	1 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)
Endom hyperpl	3 (1)	0	0	0	0	0	0	1 (<1)
Resp & thoracic	0	3 (1)	3 (1)	0	1 (<1)	1 (<1)	1 (<1)	3 (1)
COPD	0	0	0	0	0	0	0	2 (<1)
Vascular	1 (<1)	2 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response) datasets
1 MedDRA version 15.1
2 All PTs squamous cell carcinoma (in addition to squamous cell carcinoma of skin) were determined to be of the skin by narrative review

Adverse Events Leading to Withdrawal

Adverse events leading to withdrawal where at least three subjects reported the event for the system organ class or preferred term are shown in Table 131. As only AEs as the primary reason for withdrawal are reported, rather than primary and secondary, totals differ slightly from Table 1.

The percentage of subjects withdrawn for AEs was evenly balanced across treatment groups, ranging from 10 to 15% (14% in placebo). Many SOCs and PTs also showed balanced withdrawals for specific adverse events.

Although withdrawals for Cardiac SOC events were generally balance across treatment groups, withdrawals for coronary artery disease (PT) were limited to the BZA 10 mg/CE 0.625 mg and BZA 20 mg/CE 0.625 mg groups (3 and 2 subjects respectively). As

noted in the discussion of SAEs above, this finding will need to be further compared with the other clinical studies.

Reviewer's comment: It is unclear why fatigue should only cause withdrawal in the BZA 20 mg/CE 0.625 mg group (n=3 subjects). This finding is likely due to chance.

The Musculoskeletal and Connective Tissue Disease SOC showed increased withdrawals for the BZA 10 mg/CE 0.45 mg and placebo treatment groups (10 and 12 subjects respectively compared to no more than 5 in any other group). For the BZA 10 mg/CE 0.45 mg group, the increase consisted of arthralgia (4 subjects, no more than 1 in any other group) and back pain (3 subjects, no more than 1 in any other group) and is likely chance. For placebo, the increase was from osteoporosis (6 subjects, no more than 2 in any other group) and likely resulted from the lack of a bone-active agent.

The Reproductive System and Breast SOC showed a marked imbalance in withdrawals with increase in the BZA 10 mg/CE 0.625 treatment group (23 subjects, no more than 9 in any other group). This was primarily from an increase in endometrial hyperplasia (11 subjects, there were also 4 in the BZA 10 mg/CE 0.45 group but only 1 in all other groups combined) and vaginal hemorrhage (4 subjects, no more than 2 in any other group). These findings likely resulted from a lack of uterine protective effect of BZA 10 mg. The finding of breast pain leading to withdrawal in only 3 subjects in the BZA 20 mg/CE 0.45 and 1 in placebo is likely chance.

Vascular SOC withdrawals appear driven by hot flush withdrawals, which occurred primarily with raloxifene (16 subjects) and placebo (12 subjects), although 8 subjects also withdrew in the BZA 40 mg/CE 0.45 group. Given the population, hot flushes with placebo and raloxifene are expected. It appears the higher dose of bazedoxifene combined with the lower dose of conjugated estrogen may not have as great a tendency to reduce hot flushes as other active dose combinations tested.

Table 131: Trial 303 Adverse Events as Primary Reason for Withdrawal, at least 3 Subjects for the Event

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
WD for AE	66 (15)	52 (13)	49 (12)	63 (15)	46 (11)	44 (10)	59 (14)	61 (14)	0.222
Cardiac	3 (1)	4 (1)	2 (<1)	1 (<1)	2 (<1)	5 (1)	0	3 (1)	0.391
CAD	3 (1)	2 (<1)	0	0	0	0	0	0	0.027*
GI	4 (1)	3 (1)	7 (2)	10 (2)	6 (1)	6 (1)	8 (2)	6 (1)	0.623
Abd pain upr	1 (<1)	0	1 (<1)	6 (1)	3 (1)	1 (<1)	2 (<1)	3 (1)	0.120
General&ad site	3 (1)	7 (2)	4 (1)	2 (<1)	5 (1)	3 (1)	5 (1)	4 (1)	0.737
Chest pain	0	3 (1)	1 (<1)	0	2 (<1)	0	3 (1)	1 (<1)	0.226
Fatigue	0	3 (1)	0	0	0	0	0	0	0.003*
Investigations	5 (1)	4 (1)	2 (<1)	9 (2)	2 (<1)	6 (1)	4 (1)	3 (1)	0.285
Wt increased	0	2 (<1)	1 (<1)	4 (1)	0	1 (<1)	2 (<1)	1 (<1)	0.281

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
MS & CT	3 (1)	3 (1)	5 (1)	10 (2)	4 (1)	3 (1)	5 (1)	12 (3)	0.038*
Arthralgia	1 (<1)	1 (<1)	0	4 (1)	0	0	1 (<1)	0	0.042*
Back pain	1 (<1)	0	1 (<1)	3 (1)	0	1 (<1)	0	1 (<1)	0.355
Osteoporosis	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)	0	0	6 (1)	0.010*
Nervous system	7 (2)	7 (2)	3 (1)	3 (1)	4 (1)	4 (1)	4 (1)	3 (1)	0.697
Headache	1 (<1)	3 (1)	0	1 (<1)	0	3 (1)	2 (<1)	3 (1)	0.382
Psychiatric	5 (1)	3 (1)	7 (2)	2 (<1)	4 (1)	3 (1)	3 (1)	7 (2)	0.526
Depression	2 (<1)	1 (<1)	5 (1)	1 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (<1)	0.517
Rrpro & breast	23 (5)	4 (1)	3 (1)	6 (1)	9 (2)	2 (<1)	3 (1)	3 (1)	<0.001*
Breast pain	0	0	0	0	3 (1)	0	0	1 (<1)	0.028*
End hyperpl	11 (3)	1 (<1)	0	4 (1)	0	0	0	0	<0.001*
Vag hemorrh	4 (1)	1 (<1)	0	0	2 (<1)	0	0	0	0.019*
Vascular	4 (1)	3 (1)	5 (1)	7 (2)	3 (1)	9 (2)	18 (4)	15 (4)	<0.001*
Hot flush	1 (<1)	0	3 (1)	4 (1)	3 (1)	8 (2)	16 (4)	12 (3)	<0.001*

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

Adverse Events Leading to Dose Alteration

No other adverse events were found to have led to study drug discontinuation or dose reduction.

Adverse Events: On- and post-treatment

On- and post-treatment adverse events for Trial 303 which occurred in at least 5% of subjects in a treatment group are shown in Table 132. Totals differ from Table 1as AEs in the 15 day post-treatment period are included. In general, adverse events were similar between treatment groups. The SOCs with the largest number of events were Musculoskeletal and Connective Tissue Disorders (overall 63% of subjects reporting), Infections and Infestations (63%), Nervous System Disorders (50%), and Gastrointestinal Disorders (48%), The most common PTs were headache (overall 40% of subjects reporting), arthralgia (31%), back pain (29%), influenza (20%), pain in extremity (18%), myalgia (17%), nasopharyngitis (16%),, abdominal pain upper (12%). upper respiratory tract infection (12%), abdominal pain (11%), and insomnia (11%).

The Eye Disorder SOC showed increased events in placebo (43 subjects (10%), 20 to 35 subjects in other treatment groups) which on review consisted of small increases in several mostly unrelated preferred terms (especially cataract, lacrimation increased, ocular hyperemia, and vitreous floaters).

The Reproductive System and Breast Disorder SOC showed increased events in the bazedoxifene 10 mg treatment groups (36% in the BZA 10 mg/CE 0.625 mg group, 33% in the BZA 10 mg/CE 0.45 mg group, 21-27% other active treatment groups, 27% placebo). Particularly contributing to this difference were vaginal hemorrhage (6% in the BZA 10 mg/CE 0.625 mg group, 5% in the BZA 10 mg/CE 0.45 mg group, <1-3% other active treatment groups, 2% placebo), endometrial hyperplasia (5% in the BZA 10

mg/CE 0.625 mg group, 2% in the BZA 10 mg/CE 0.45 mg group, 0-<1% other active treatment groups, <1% placebo), vaginal discharge (4% in the BZA 10 mg/CE 0.625 mg group, 4% in the BZA 10 mg/CE 0.45 mg group, 1-3% other active treatment groups, 2% placebo), and genital discharge (8% in the BZA 10 mg/CE 0.625 mg group, 8% in the BZA 10 mg/CE 0.45 mg group, 5-7% other active treatment groups, 6% placebo). Vulvovaginal pruritis was also increased in the raloxifene group (4% in the BZA 10 mg/CE 0.625 mg group, 5% in the BZA 10 mg/CE 0.45 mg group, 1-2% other BZA/CE groups, 4% raloxifene group, 3% placebo). These findings were likely largely secondary to lack of uterine protective effect with bazedoxifene 10 mg.

Uterine polyps were more common in all conjugated estrogen treatment groups except the BZA 40 mg/CE 0.45 mg group (BZA 40 mg/CE 0.45 mg group 2 subjects (<1%), other BZA/CE groups 4-11 subjects (1-3%), Raloxifene no subjects, placebo 2 subjects (<1%)). Uterine polyps have been associated with estrogen use.

In the Infections and infestations SOC, the preferred term respiratory tract infection predominated in the BZA 10 mg/CE 0.625 mg group (15 subjects, 3%) and placebo group (14 subjects, 3%) with no more than 10 subjects in any other treatment group. The terms upper respiratory tract infection and bronchitis did not show similar patterns. The association is likely chance.

Also in the Infections and infestations SOC, the preferred term vulvovaginal candidiasis predominated in the BZA 10 mg/CE 0.625 mg group (25 subjects, 6%), BZA 10 mg/CE 0.45 mg group (22 subjects, 5%), and BZA 20 mg/CE 0.625 mg group (18 subjects, 4%) with no more than 14 subjects in any other treatment group. A similar pattern but fewer subjects are seen with the preferred terms vulvovaginal mycotic infection, vulvovaginitis, and candidiasis. As conjugated estrogen is associated with vaginal candidiasis, this finding is expected. It appears increasing doses of bazedoxifene may be associated with less candidiasis.

The preferred term fall was lower in the BZA 10 mg/CE 0.625 mg group (4 subjects, 1%, 8 to 21 subjects in the other groups with 15 subjects in placebo). This finding was likely due to chance.

Laboratory adverse events are discussed below.

Ultrasound uterus abnormal was reported most commonly in the bazedoxifene 10 with conjugated estrogen groups (10 subjects (2%) in the BZA 10 mg/CE 0.625 mg group, 3 subjects (1%) in the BZA 20 mg/CE 0.625 mg group, no subjects in the BZA 40 mg/CE 0.625 mg group, 7 subjects (2%) in the BZA 10 mg/CE 0.45 mg group, 5 subjects (1%) in the BZA 20 mg/CE 0.45 mg group, 1 subject (<1%) in the BZA 40 mg/CE 0.45 mg group, no subjects in the raloxifene group, 1 subject (<1%) in the placebo group). This is consistent with a lack of uterine protection with 10 mg bazedoxifene.

The preferred term bursitis was higher in the raloxifene group (9 subjects, 2%, 0 to 5 subjects in the other groups with 1 subject in placebo).

The preferred term muscle spasm was lower in the placebo group (23 subjects, 5%, 31 to 51 subjects in the other groups). As muscle spasms have been reported with both conjugated estrogens and raloxifene, this finding is expected.

The preferred term osteoporosis was higher in the placebo group (15 subjects, 4%, 1 to 9 subjects in the other groups). As the placebo group is the only group not taking a product which is effective in preventing or treating osteoporosis, this finding is not surprising.

Alopecia may be associated with the combination product (7 to 16 subjects (2-4%) in the BZA/CE groups, 4 and 6 subjects (both 1%) in the raloxifene and placebo groups respectively). Alopecia has been associated with estrogen use.

There may be a slight increase in urticaria with the combination product (1 to 9 subjects (<1-2%) in the BZA/CE groups, 1 subject (<1%) each in the raloxifene and placebo groups). This will be further compared with other clinical studies.

Hot flushes, not surprisingly, may be more frequent in the raloxifene and placebo groups (13 to 20 subjects (3-5%) in the BZA/CE groups, 31 subjects (7%) in the raloxifene group and 25 subjects (6%) in the placebo group).

Table 132: Trial 303 On- and Post-treatment Adverse Events Reported by at least 5% of Subjects in a Treatment Group

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Any AE	409(95)	393(95)	399(96)	408(95)	414(96)	393(93)	400(95)	404(95)	0.722
Cardiac	24 (6)	20 (5)	25 (6)	19 (4)	32 (7)	27 (6)	20 (5)	25 (6)	0.607
Ear & labyrinth	30 (7)	44 (11)	45 (11)	43 (10)	43 (10)	44 (10)	33 (8)	45 (11)	0.425
Vertigo	9 (2)	23 (6)	28 (7)	24 (6)	26 (6)	22 (5)	20 (5)	23 (5)	0.119
Eye	25 (6)	32 (8)	21 (5)	27 (6)	32 (7)	35 (8)	20 (5)	43 (10)	0.037*
GI	202(47)	184(44)	206(49)	214(50)	228(53)	202(48)	215(51)	195(46)	0.259
A. pain	60 (14)	42 (10)	44 (11)	43 (10)	58 (13)	42 (10)	41 (10)	35 (8)	0.105
A. pain upper	48 (11)	54 (13)	56 (13)	59 (14)	58 (13)	55 (13)	46 (11)	40 (9)	0.438
Constipation	29 (7)	32 (8)	34 (8)	34 (8)	34 (8)	30 (7)	43 (10)	29 (7)	0.667
Diarrhea	29 (7)	30 (7)	32 (8)	36 (8)	44 (10)	34 (8)	37 (9)	27 (6)	0.527
Dyspepsia	48 (11)	31 (7)	35 (8)	31 (7)	50 (12)	41 (10)	43 (10)	43 (10)	0.247
Flatulence	27 (6)	23 (6)	27 (6)	18 (4)	21 (5)	15 (4)	20 (5)	19 (4)	0.483
Nausea	33 (8)	35 (8)	32 (8)	33 (8)	47 (11)	31 (7)	26 (6)	25 (6)	0.192
Toothache	19 (4)	12 (3)	23 (6)	18 (4)	24 (6)	7 (2)	23 (5)	18 (4)	0.055
Vomiting	18 (4)	17 (4)	18 (4)	22 (5)	21 (5)	17 (4)	20 (5)	17 (4)	0.989
Gen & ad site	122(28)	126(30)	118(28)	123(29)	130(30)	126(30)	132(31)	136(32)	0.926
Chest pain	17 (4)	23 (6)	11 (3)	19 (4)	22 (5)	22 (5)	30 (7)	22 (5)	0.159
Fatigue	25 (6)	26 (6)	32 (8)	35 (8)	29 (7)	26 (6)	25 (6)	29 (7)	0.850

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Edema periph	32 (7)	27 (7)	29 (7)	30 (7)	35 (8)	33 (8)	28 (7)	34 (8)	0.977
Pain	32 (7)	27 (7)	26 (6)	27 (6)	28 (6)	27 (6)	25 (6)	20 (5)	0.883
Immune system	31 (7)	38 (9)	36 (9)	28 (7)	47 (11)	27 (6)	32 (8)	30 (7)	0.207
Seasonal aller	18 (4)	24 (6)	20 (5)	20 (5)	29 (7)	17 (4)	18 (4)	19 (4)	0.593
Infect & infest	287(67)	260(63)	258(62)	274(64)	283(65)	243(57)	256(61)	265(62)	0.161
Influenza	77 (18)	79 (19)	73 (18)	82 (19)	100(23)	91 (22)	96 (23)	93 (22)	0.264
Nasopharyng	72 (17)	77 (19)	66 (16)	70 (16)	80 (18)	57 (13)	61 (14)	69 (16)	0.448
Sinusitis	43 (10)	46 (11)	44 (11)	39 (9)	32 (7)	28 (7)	40 (9)	45 (11)	0.260
URI	53 (122)	44 (11)	40 (10)	47 (11)	53 (12)	48 (11)	58 (14)	48 (11)	0.718
UTI	37 (9)	43 (10)	45 (11)	42 (10)	43 (10)	34 (8)	37 (9)	38 (9)	0.865
Vv candidias	25 (6)	18 (4)	11 (3)	22 (5)	8 (2)	9 (2)	11 (3)	14 (3)	0.008*
Injury,pois,comp	82 (19)	84 (20)	77 (18)	91 (21)	74 (17)	62 (15)	87 (21)	90 (21)	0.195
Investigations	137(32)	142(34)	124(30)	133(31)	145(33)	128(30)	140(33)	128(30)	0.760
Chol increased	20 (5)	23 (6)	11 (3)	22 (5)	20 (5)	11 (3)	18 (4)	30 (7)	0.042*
BP increased	13 (3)	22 (5)	17 (4)	19 (4)	18 (4)	18 (4)	20 (5)	14 (3)	0.774
TG increased	27 (6)	24 (6)	25 (6)	20 (5)	26 (6)	18 (4)	22 (5)	17 (4)	0.704
PAP abn	24 (6)	22 (5)	10 (2)	20 (5)	23 (5)	15 (3)	23 (5)	17 (4)	0.272
Wt increased	25 (6)	25 (6)	20 (5)	20 (5)	27 (6)	21 (5)	27 (6)	21 (5)	0.893
Metab & nutrit	76 (18)	69 (17)	70 (17)	76 (18)	67 (15)	63 (15)	67 (16)	71 (17)	0.951
Hyperchol	34 (8)	35 (8)	26 (6)	39 (9)	24 (5)	29 (7)	33 (8)	37 (9)	0.472
HyperTG	38 (9)	32 (8)	39 (9)	29 (7)	32 (7)	26 (6)	27 (6)	24 (6)	0.372
MS & CT	264(61)	271(65)	248(59)	282(66)	281(65)	257(61)	271(64)	278(65)	0.383
Arthralgia	118(27)	129(31)	110(26)	129(30)	129(30)	147(35)	139(33)	142(33)	0.114
Back pain	128(30)	132(32)	111(27)	140(33)	130(30)	110(26)	121(29)	115(27)	0.286
Muscle spasms	48 (11)	31 (7)	50 (12)	47 (11)	51 (12)	45 (11)	38 (9)	23 (5)	0.011*
Myalgia	76 (18)	74 (18)	67 (16)	73 (17)	75 (17)	64 (15)	75 (18)	73 (17)	0.967
Neck pain	26 (6)	30 (7)	32 (8)	36 (8)	32 (7)	23 (5)	40 (9)	26 (6)	0.344
Pain in extrem	75 (17)	72 (17)	76 (18)	88 (20)	83 (19)	70 (17)	80 (19)	80 (19)	0.883
Neoplasm	16 (4)	22 (5)	17 (4)	30 (7)	29 (7)	22 (5)	24 (6)	24 (6)	0.385
Nervous system	220(51)	196(47)	199(48)	216(50	218(50)	215(51)	207(49)	230(54)	0.642
Dizziness	18 (4)	19 (5)	17 (4)	26 (6)	37 (9)	22 (5)	23 (5)	22 (5)	0.101
Headache	182(42)	167(40)	157(38)	179(42)	163(38)	163(39)	170(40)	169(40)	0.808
Migraine	22 (5)	16 (4)	15 (4)	12 (3)	24 (6)	17 (4)	11 (3)	15 (4)	0.295
Sinus h/a	19 (4)	20 (5)	22 (5)	16 (4)	27 (6)	17 (4)	16 (4)	20 (5)	0.677
Psychiatric	108(25)	100(24)	92 (22)	89 (21)	110(25)	108(26)	121(29)	118(28)	0.141
Anxiety	25 (6)	25 (6)	25 (6)	28 (7)	24 (6)	35 (8)	30 (7)	25 (6)	0.777
Depression	30 (7)	42 (10)	29 (7)	29 (7)	37 (9)	33 (8)	38 (9)	38 (9)	0.562
Insomnia	50 (12)	33 (8)	39 (9)	36 (8)	49 (11)	45 (11)	55 (13)	57 (13)	0.086
Renal & urinary	45 (10)	44 (11)	47 (11)	48 (11)	42 (10)	37 (9)	42 (10)	47 (11)	0.936
Repro & breast	155(36)	102(25)	99 (24)	143(33)	118(27)	101(24)	89 (21)	114(27)	<.001*
Breast pain	10 (2)	10 (2)	16 (4)	20 (5)	27 (6)	15 (4)	15 (4)	17 (4)	0.080
Gen discharge	35 (8)	26 (6)	27 (6)	34 (8)	23 (5)	29 (7)	27 (6)	27 (6)	0.770
Vag hemorrha	25 (6)	6 (1)	6 (1)	21 (5)	13 (3)	5 (1)	2 (<1)	9 (2)	<.001*
Resp,thor,media	111(26)	107(26)	94 (23)	118(27)	127(29)	114(27)	114(27)	105(25)	0.505
Cough	33 (8)	39 (9)	41 (10)	35 (8)	42 (10)	43 (10)	40 (9)	39 (9)	0.916
Orophar pain	44 (10)	43 (10)	37 (9)	36 (8)	49 (11)	37 (9)	46 (11)	41 (10)	0.794
Skin & subcut	106(25)	89 (21)	98 (24)	96 (22)	104(24)	90 (21)	78 (18)	88 (21)	0.414
Vascular	79 (18)	76 (18)	71 (17)	84 (20)	73 (17)	74 (17)	81 (19)	81 (19)	0.960
Hot flush	17 (4)	14 (3)	15 (4)	16 (4)	13 (3)	20 (5)	31 (7)	25 (6)	0.035*
Hypertension	47 (11)	42 (10)	39 (9)	49 (11)	45 (10)	34 (8)	31 (7)	42 (10)	0.471

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
1 P-value for Chi-square 2 MedDRA version 15.1									

Adverse Events of Special Interest:

Venous Thromboembolism (VTE)

Venous thromboembolism has been a concern both with estrogens and bazedoxifene monotherapy. Venous thromboembolism events reported in Trial 303 are listed in Table 133. No retinal vein thrombosis events were reported in this trial.

A slight excess of total events of venous thromboembolism may have occurred in the BZA 40 mg/CE 0.625 mg group, which is the highest dose of both drugs used in the combination product tested (6 events, compared to 3 in placebo), but numbers are small and no other treatment group appears to have what could be considered an excess of events. The next highest group for total events is the BZA 10 mg/CE 0.45 group, the lowest dose of both drugs tested, at 4 events. The doses considered for registration, BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg, showed 0 and 1 event respectively.

In the WHI estrogen alone substudy, the DVT rate on CEs was 23 per 10,000 woman years compared to 15 for placebo. For the estrogen plus progestin substudy, rates were 26 and 13 respectively. In this study, considering each treatment group had a mean of 425 subjects with a mean completion rate of 66%, and assuming linear dropout over the 2 years of the study, each treatment group represents about 700 woman years of treatment. Using the lowest placebo rate of 13 per 10,000 woman years, 0.9 events would be expected over the study per treatment group, with up to double that in the active treatment groups. The one DVT event reported in placebo is thus about what is expected. The two DVT events reported in 6 treatment groups is considerably below what is expected in the BZA/CE groups.

In the MORE Study over 2.6 years, venous thromboembolism (VTE, defined as deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) was reported in about 1 in 100 patients treated with raloxifene (rate 38 per 10,000 woman years) which was more than double the placebo rate. The raloxifene group would be expected to have 2.7 VTE events or more, as VTE events with raloxifene are reportedly more common during the initial months of therapy. No VTE events as defined were reported in this study with raloxifene, which raises concerns for underreporting of VTE events for the combination product as well.

Table 133: Trial 303 Venous Thromboembolism Events Reported On- and Post-Treatment

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Pulm embolus	0	0	1 (<1)	0	0	0	0	0	0.414
DVT	1 (<1)	0	1 (<1)	0	0	0	0	1 (<1)	0.659
Phlebitis	0	1 (<1)	2 (<1)	2 (<1)	0	0	2 (<1)	1 (<1)	0.531
Phlebitis, sup	1 (<1)	0	1 (<1)	1 (<1)	0	2 (<1)	0	0	0.514
Tphlebitis	1 (<1)	0	0	0	0	0	0	1 (<1)	0.548
Tphlebitis,sup	0	0	1 (<1)	1 (<1)	0	0	0	0	0.537
Venous throm	0	0	0	0	0	1 (<1)	0	0	0.425

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

A peripheral artery thrombus was also reported in a 65 year old woman in the BZA 10 mg/CE 0.45 mg treatment group. On Day 535, study drug was discontinued due to dyspnea and signs of congestion on chest x-ray. On Day 538 the subject underwent a right upper limb thromboembolectomy for acute arterial occlusion with right arm numbness and cyanosis. The subject withdrew from the study.

Cerebrovascular Events

Cerebrovascular events have been a concern both with estrogens and bazedoxifene monotherapy. Cerebrovascular events reported in Trial 303 are listed in Table 134.

Except for syncope, cerebrovascular events were quite uncommon. If only the more definite preferred terms of cerebral hemorrhage, cerebral infarction, CVA, and TIA are considered, 3 events were reported in the BZA 10 mg/CE 0.625 mg group, no events in the BZA 20 mg/CE 0.625 mg group, 2 events in the BZA 40 mg/CE 0.625 mg group, 1 event in the BZA 10 mg/CE 0.45 mg group, 1 event in the BZA 20 mg/CE 0.45 mg group, 1 event in the BZA 40 mg/CE 0.45 mg group, and no events with either raloxifene or placebo. A concern exists for a continued small risk of cerebrovascular disease with the BZA/CE product. Raloxifene, an agent known to induce stroke, had only 3 episodes of syncope reported for cerebrovascular events in this study.

In the WHI estrogen alone substudy, the all stroke rate on CEs was 45 per 10,000 woman years compared to 33 for placebo. For the estrogen plus progestin substudy, rates were 33 and 25 respectively. TIAs were not included. As calculated in the VTE discussion above, each treatment group represents about 700 woman years of treatment. Using the lowest placebo rate of 25 per 10,000 woman years, 1.8 events would be expected over the study per treatment group, with up to 180% of that (3.2 events) in the active treatment groups. As only three of the BZA/CE groups report single stroke events with none reported in placebo, stroke reports were considerably below

what would be expected both for BZA/CE treatment groups and placebo (and raloxifene).

Table 134: Trial 303 Cerebrovascular Events Reported On- and Post-Treatment

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Carotid art dis	0	1 (<1)	0	0	0	0	0	0	0.408
Carotid art stn	1 (<1)	0	0	0	0	0	0	0	0.439
Cereb hemorr	1 (<1)	0	0	0	0	0	0	0	0.439
Cereb infract	0	0	0	0	1 (<1)	0	0	0	0.445
CVA	0	0	0	1 (<1)	0	0	0	0	0.439
Loss of consc	1 (<1)	0	0	0	0	0	0	1 (<1)	0.548
Syncope	3 (1)	0	4 (1)	2 (<1)	4 (1)	2 (<1)	3 (1)	6 (1)	0.401
TIA	2 (<1)	0	2 (<1)	0	0	1 (<1)	0	0	0.221

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

A 55 year old woman assigned to the BZA 20 mg/CE 0.625 mg treatment group reported weakness in the right arm on Day 312, which resolved spontaneously on Day 338. Reportedly there was no relevant medical history or prior medications. No additional testing or evaluation was reported. In COSTART, this was originally coded as paresis, and in MedDRA is now coded as muscle weakness, but this event could represent a cerebral ischemic event. The subject completed the study.

For a 60 year old woman in the BZA 40 mg/CE 0.45 mg group, an event of circulatory disturbance (lack of memory) with a start date of 28-Feb-04 (Day 151) was recorded in the source documentation, however, the event was recorded as forgetfulness (start date 28- Feb-04) and memory decreased (start date 28-Feb-04, stop date 4-Jul-05) on the CRF. The subject was reportedly overweight and had hypertension treated with captopril. No additional testing or evaluation was reported. This could represent a CVA. The subject completed the study. The error in recording was found in a regulatory authority investigator site inspection of Site 447. The Agency was informed about this in a submission of May 23, 2013 in Errata 2 to the study report for Trial 303.

Cardiac Ischemia Events

Overall cardiac disorders and potential cardiac ischemic events are listed in Table 135. The Cardiac Disorders SOC is balanced between treatment groups. Although the preferred term of coronary artery disease is confined largely to the CE 0.625 mg treatment groups and especially the BZA 10 mg/CE 0.625 mg group with 4 subjects reporting events, more angina is reported in the CE 0.45 mg groups and MIs are few and not concentrated in any treatment group.

Narratives for subjects reporting chest pain were reviewed. Reported work-up was quite variable and often results of tests known to have been done by consultants were not available. Most subjects had at least an end of study ECG per protocol which could be compared to the ECG at Screening. To the extent work-up was performed and reported, a cardiac etiology for the chest pain in these subjects was not suspected unless also reported in a cardiac ischemic category with the possible exception of a 58 year old woman in the raloxifene group discontinued at Sponsor request at Day 52 because of ECG changes at Screening suggestive of myocardial ischemia.

Table 135: Trial 303 Potential Cardiac Ischemic Events On- and Post-Treatment

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Cardiac	24 (6)	20 (5)	25 (6)	19 (4)	32 (7)	27 (6)	20 (5)	25 (6)	0.607
Angina pector	0	1 (<1)	0	2 (<1)	1 (<1)	1 (<1)	0	0	0.523
CAD	4 (1)	2 (<1)	1 (<1)	0	1 (<1)	0	0	0	0.052
CA insuff	0	0	0	0	0	0	0	1 (<1)	0.433
MI	0	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0.657
Chest discom	1 (<1)	4 (1)	4 (1)	2 (<1)	5 (1)	7 (2)	4 (1)	5 (1)	0.525
Chest pain	17 (4)	23 (6)	11 (3)	19 (4)	22 (5)	22 (5)	30 (7)	22 (5)	0.159
Non-card c p	0	1 (<1)	2 (<1)	5 (1)	4 (1)	3 (1)	2 (<1)	5 (1)	0.301

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

A 60 year old overweight woman in the BZA 20 mg/CE 0.45 mg treatment group with a 60 pack year smoking history and elevated cholesterol and triglycerides had a normal ECG at screening and an ECG on study completion demonstrating an inferior wall MI of uncertain age. A stress echocardiogram by a cardiologist showed impaired exercise tolerance, wall motion abnormalities consistent with ischemia, and left ventricular systolic dysfunction. This silent MI is not included in Table 8.

Malignancy

Malignancies and potential malignancies reported in Trial 303 are shown in Table 136 where at least one treatment group has at least 2 subjects reporting that preferred term. The Neoplasm SOC is balanced between treatment groups. For preferred terms, overall little difference is noted between treatment groups. A single case of endometrial cancer was reported in the BZA 20 mg/CE 0.45 mg group and a uterine neoplasm in the BZA 10 mg/CE 0.45 mg group. A case of ovarian cancer was reported in the BZA 40 mg/CE 0.625 mg group and a case of ovarian epithelial cancer in the BZA 10 mg/CE 0.45 mg group.

Table 136: Trial 303 Malignancies and Potential Malignancies Reported, at least 2 Subjects in a Treatment Group

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Neoplasm	16 (4)	22 (5)	17 (4)	30 (7)	29 (7)	22 (5)	24 (6)	24 (6)	0.385
Basal cell ca	3 (1)	2 (<1)	1 (<1)	3 (1)	1 (<1)	1 (<1)	2 (<1)	3 (1)	0.891
Breast ca[3]	0	0	1 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)	
Br neoplasm	3 (1)	5 (1)	0	1 (<1)	4 (1)	5 (1)	2 (<1)	2 (<1)	0.274
Lung neopl	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	0	0.328
Neoplasm	0	2 (<1)	1 (<1)	0	0	0	0	2 (<1)	0.214
Sq cell ca[4]	0	0	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	2 (<1)	
Thyroid neo	1 (<1)	2 (<1)	4 (1)	2 (<1)	2 (<1)	4 (1)	1 (<1)	1 (<1)	0.624

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 Combined PTs breast cancer, breast cancer female, and breast cancer stage II
4 Combined PTs squamous cell carcinoma and squamous cell carcinoma of the skin All were determined to be of the skin by narrative review

Breast Disorders Reported as Adverse Events

Breast disorders reported as adverse events in Trial 303 are shown in Table 137 where at least one treatment group has at least 2 subjects reporting that preferred term. Breast pain was also a secondary efficacy endpoint. On-treatment mammograms were done at Months 12 and 24.

Breast adverse events appear generally balanced between treatment groups. Breast pain was found to be perhaps slightly less common in the BZA 10 mg/CE 0.625 mg and BZA 20 mg/CE 0.625 mg treatment groups (10 subjects in each reporting (2%)), and more common in the BZA 20 mg/CE 0.45 mg treatment groups (27 subjects (6%)), with 15 to 20 subjects in other active treatment groups (4-5%) and 17 subjects (4%) in placebo. It is difficult to explain this pattern other than by attributing it to chance. As noted above, breast pain measured as efficacy showed no difference between the BZA/CE groups and either placebo or raloxifene. Fibrocystic breast disease may be slightly more common in the BZA/CE groups (0 to 3 subjects, 0-1%, no subjects with raloxifene or placebo). This will be further compared to other clinical studies.

Table 137: Trial 303 Breast Disorders Reported as Adverse Events, at least 2 Subjects in a Treatment Group

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Mammogr abn	10 (2)	10 (2)	9 (2)	11 (3)	8 (2)	15 (3)	4 (1)	6 (1)	0.275
Breast ca[3]	0	0	1 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)	
Br neoplasm	3 (1)	5 (1)	0	1 (<1)	4 (1)	5 (1)	2 (<1)	2 (<1)	0.274
Breast cyst	3 (1)	0	1 (<1)	2 (<1)	2 (<1)	0	0	1 (<1)	0.359

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
Br discharge	1 (<1)	0	0	1 (<1)	1 (<1)	0	0	2 (<1)	0.528
Br discomfor	0	1 (<1)	0	0	1 (<1)	0	2 (<1)	0	0.328
Br disorder[4]	2 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	0	3 (1)	
Br enlarge	1 (<1)	3 (1)	3 (1)	4 (1)	3 (1)	1 (<1)	1 (<1)	4 (1)	0.684
Br mass	1 (<1)	2 (<1)	0	2 (<1)	0	2 (<1)	1 (<1)	0	0.531
Breast pain	10 (2)	10 (2)	16 (4)	20 (5)	27 (6)	15 (4)	15 (4)	17 (4)	0.080
Br swelling	0	1 (<1)	2 (<1)	0	0	0	1 (<1)	1 (<1)	0.498
Br tender	1 (<1)	2 (<1)	0	3 (1)	4 (1)	2 (<1)	0	1 (<1)	0.301
Fibrocyst bd	3 (1)	0	1 (<1)	0	0	2 (<1)	0	0	0.083

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 Combined PTs breast cancer, breast cancer female, and breast cancer stage II
4 Combined PTs breast disorder and breast disorder female

Uterine Disorders Reported as Adverse Events

Salient features of uterine disorders reported as adverse events are discussed in the Reproductive System and Breast Disorder SOC discussion under Adverse Events above. Several uterine and vaginal measures including endometrial hyperplasia, vaginal atrophy, dyspareunia, and bleeding were measured as efficacy measures.

Endometrial biopsy was performed in all subjects at Screening and Months 6, 12, and 24, and is discussed in the review of uterine safety. Transvaginal ultrasound was performed in about a third of subjects at Screening and Months 12 and 24, and is also discussed in the uterine safety review. At sites performing TVUs, if the ultrasound at Month 12 or 24 identified non-measurable endometrium, double-wall thickness greater than 8 mm, or a focal abnormality, hysteroscopy with directed biopsy was performed in place of the routine biopsy.

Fractures

Fractures were collected as adverse events in Trial 303. No scheduled spine or other x-rays were done. The population consisted of women age 40 to 75 at least 12 months postmenopausal. In addition, about 40% of the population were greater than 5 years postmenopausal, had a lumbar spine or total hip T-score of -1.0 to -2.5, and had at least one other risk factor for osteoporosis. Another approximately 25% of the population was between 1 and 5 years postmenopausal and had at least one other risk factor for osteoporosis.

Fractures were generally balanced between groups (Table 138). The isolated increase in hand fractures in the BZA 10 mg/CE 0.45 mg group is likely a chance occurrence. The BZA 10 mg/CE 0.45 mg group overall showed one of the larger increases in BMD at the lumbar spine, total hip, and distal radius, so loss of BMD is probably not involved. This trial is not designed to evaluate fracture risk.

Table 138: Trial 303 Fractures Reported as AEs in Trial 303

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Ankle fx	2 (<1)	1 (<1)	2 (<1)	1 (<1)	0	3 (1)	1 (<1)	3 (1)	0.675
Clavicle fx	2 (<1)	0	0	0	0	0	0	0	0.055
Compress fx	1 (<1)	0	0	0	0	0	0	0	0.439
Fem neck fx	0	0	0	0	0	0	1 (<1)	0	0.425
Fibula fx	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	0.777
Foot fx	4 (1)	1 (<1)	5 (1)	5 (1)	7 (2)	2 (<1)	4 (1)	5 (1)	0.559
Fracture	1 (<1)	1 (<1)	0	3 (1)	0	1 (<1)	2 (<1)	2 (<1)	0.547
Hand fx	1 (<1)	0	0	4 (1)	0	0	2 (<1)	0	0.019*
Humerus fx	0	0	0	1 (<1)	0	0	0	0	0.439
Jaw fx	0	0	0	0	0	0	1 (<1)	0	0.425
L limb fx	0	0	2 (<1)	0	0	1 (<1)	2 (<1)	1 (<1)	0.382
Open fx	0	0	1 (<1)	0	0	0	0	0	0.414
Pubis fx	0	0	0	0	1 (<1)	0	0	0	0.445
Radius fx	0	1 (<1)	1 (<1)	0	0	1 (<1)	0	0	0.644
Rib fx	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (1)	1 (<1)	0	0	0.545
Sp comp fx	1 (<1)	0	0	0	0	0	0	0	0.439
Sternal fx	0	0	1 (<1)	0	0	0	0	0	0.414
Ulna fx	0	0	1 (<1)	0	0	0	0	0	0.414
Up limb fx	0	0	2 (<1)	2 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0.589
Wrist fx	2 (<1)	2 (<1)	2 (<1)	2 (<1)	1 (<1)	0	4 (1)	1 (<1)	0.597
Summed fx	17	8	18	19	13	9	19	14	

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

Laboratory:

Laboratory Adverse Events

Laboratory events in Trial 303 reported as adverse events are shown in Table 139 where at least 3 subjects in a treatment group had that adverse event.

The preferred term aspartate aminotransferase increased was reported more often in the raloxifene group (15 subjects, 4%, 2 to 11 subjects in the other groups with 8 subjects in placebo. The preferred term alanine aminotransferase increased was also higher in the raloxifene group (16 subjects, 4%, 4 to 10 subjects in the other active treatment groups with 11 subjects in placebo). There did not appear to be a tendency for these preferred terms to be more common with the combination product. Bazedoxifene monotherapy has been associated with increased transaminases, but that is not noted in this study.

Cholesterol and triglycerides were checked in all subjects with the chemistry panel at Screening, every 3 months during the first year of the study, and every 6 months during the second year. HDL and LDL cholesterol were checked yearly. Lipid parameters including cholesterol, HDL, LDL, and VLDL cholesterol, triglycerides, VLDL triglycerides, HDL-2 and -3 cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein (a) were

checked at Screening, Baseline, and every 6 months in this study in the Osteoporosis Prevention II Substudy, about 25% of the population. Blood cholesterol increased was reported most commonly in the placebo group (20 subjects (5%) in the BZA 10 mg/CE 0.625 mg group, 23 subjects (6%) in the BZA 20 mg/CE 0.625 mg group, 11 subjects (3%) in the BZA 40 mg/CE 0.625 mg group, 22 subjects (5%) in the BZA 10 mg/CE 0.45 mg group, 20 subjects (5%) in the BZA 20 mg/CE 0.45 mg group, 11 subjects (3%) in the BZA 40 mg/CE 0.45 mg group, 18 subjects (4%) in the raloxifene group, 30 subjects (7%) in the placebo group). Hypercholesterolemia was reported in similar percentages of subjects across treatment groups.

Estrogen therapy has been associated with increased triglyceride levels. The preferred terms hypertriglyceridemia and triglycerides increased are generally more common with the combination product than placebo (6 to 9% of combination product groups, 6% in placebo and 4 to 6% of combination product groups, 4% placebo respectively).

Table 139: Trial 303 Laboratory Events Reported as Adverse Events, at least 3 Subjects in a Treatment Group

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=430	N=414	N=417	N=430	N=433	N=423	N=423	N=427	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Blood & lymph									
Anemia	4 (1)	4 (1)	5 (1)	10 (2)	7 (2)	4 (1)	7 (2)	3 (1)	0.455
Eosinophlia	0	1 (<1)	2 (<1)	4 (1)	1 (<1)	4 (1)	3 (1)	1 (<1)	0.331
Leukopenia	3 (1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	2 (<1)	0	0.550
Thrombocytop	1 (<1)	2 (<1)	1 (<1)	3 (1)	4 (1)	2 (<1)	1 (<1)	2 (<1)	0.796
Endocrine									
Hypothyroid	10 (2)	4 (1)	7 (2)	6 (1)	11 (3)	4 (1)	7 (2)	8 (2)	0.540
Investigations									
ALT increased	7 (2)	8 (2)	9 (2)	10 (2)	6 (1)	4 (1)	16 (4)	11 (3)	0.148
AST increased	10 (2)	5 (1)	11 (3)	2 (<1)	6 (1)	5 (1)	15 (4)	8 (2)	0.026*
Alk Phos incr	2 (<1)	0	1 (<1)	2 (<1)	2 (<1)	1 (<1)	3 (1)	2 (<1)	0.831
Chol increased	20 (5)	23 (6)	11 (3)	22 (5)	20 (5)	11 (3)	18 (4)	30 (7)	0.042*
Glucose incr	1 (<1)	5 (1)	2 (<1)	5 (1)	5 (1)	5 (1)	9 (2)	6 (1)	0.263
Potassium incr	3 (1)	0	2 (<1)	3 (1)	1 (<1)	4 (1)	0	1 (<1)	0.265
TSH decrease	0	1 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	4 (1)	0.527
TSH increased	4 (1)	6 (1)	3 (1)	3 (1)	10 (2)	4 (1)	5 (1)	7 (2)	0.391
TG increased	27 (6)	24 (6)	25 (6)	20 (5)	26 (6)	18 (4)	22 (5)	17 (4)	0.704
BUN increase	1 (<1)	3 (1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	4 (1)	0.596
Uric acid incr	5 (1)	6 (1)	5 (1)	4 (1)	4 (1)	1 (<1)	5 (1)	6 (1)	0.763
Blood urine pr	2 (<1)	0	4 (1)	1 (<1)	0	3 (1)	2 (<1)	3 (1)	0.325
CRP increased	3 (1)	2 (<1)	0	0	1 (<1)	2 (<1)	1 (<1)	0	0.341
LDL increased	6 (1)	8 (2)	2 (<1)	2 (<1)	7 (2)	7 (2)	8 (2)	10 (2)	0.228
Transamin incr	0	3 (1)	0	3 (1)	2 (<1)	1 (<1)	0	0	0.118
WBC decrease	0	1 (<1)	3 (1)	2 (<1)	1 (<1)	0	2 (<1)	0	0.330
WBC increase	2 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	4 (1)	0	0	0.396
Metab & nutrit									
Dyslipidemia	1 (<1)	1 (<1)	5 (1)	3 (1)	0	1 (<1)	0	1 (<1)	0.058
Hyperchol	34 (8)	35 (8)	26 (6)	39 (9)	24 (5)	29 (7)	33 (8)	37 (9)	0.472
Hyperglycem	6 (1)	3 (1)	8 (2)	3 (1)	4 (1)	2 (<1)	5 (1)	4 (1)	0.528
Hyperlipidem	5 (1)	2 (<1)	2 (<1)	3 (1)	1 (<1)	1 (<1)	8 (2)	5 (1)	0.086

SOC PT[2]	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
HyperTG	38 (9)	32 (8)	39 (9)	29 (7)	32 (7)	26 (6)	27 (6)	24 (6)	0.372
Hyperuricemia	2 (<1)	2 (<1)	1 (<1)	3 (1)	0	2 (<1)	0	2 (<1)	0.621
Renal & urinary									
Hematuria	8 (2)	15 (4)	8 (2)	15 (3)	7 (2)	14 (3)	13 (3)	10 (2)	0.374
Leukocyturia	2 (<1)	3 (1)	1 (<1)	2 (<1)	0	0	2 (<1)	2 (<1)	0.606

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

Marked Laboratory Abnormalities

Laboratory values of potential clinical importance were predetermined. In general, the number of subjects with specific laboratory events of potential clinical significance was similar between treatment groups. Total bilirubin increase >1.7 mg/dL was more common in the placebo group (8 subjects (2%) in placebo and 1-3 subjects (<1-1%) in other treatment groups). AST increase >50% above normal range was similar between groups (8 subjects (2%) in placebo and 5-12 subjects (1-3%) in other treatment groups). ALT increase > 2 times ULN was highest in the raloxifene group (3 subjects (1%) in placebo, 10 subjects (2%) in raloxifene, and 2-8 subjects (>1-2%) in other treatment groups).

Cholesterol increase >50 mg/dL to >200 mg/dL was more common in the placebo group (32 subjects (8%) in placebo and 15-26 subjects (4-6%) in other treatment groups). Triglyceride increase >50 mg/dL to >250 mg/dL was more common in the combination product group and raloxifene group (88 subjects (22%) in placebo, 119-148 subjects (30-38%) in combination product treatment groups, and 116 subjects (30%) in raloxifene). Estrogen therapy has been associated with increased triglyceride levels.

The coagulation parameters prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III activity, protein C activity, protein S activity, plasminogen activity, plasminogen activator inhibitor-1 activity, plasminogen activator inhibitor-1 antigen, and D-dimer were checked at Screening, Baseline, and every 6 months in this study in the Osteoporosis Prevention II Substudy, about 25% of the population. No definitions for laboratory values of potential clinical importance were found for these tests. Few abnormalities were noted, but most of those were in the combination product groups (2-6 subjects (2-6%) per group compared to 1 (1%) for raloxifene and none for placebo). Plasminogen activity increase had the most abnormal values reported with no subjects reported in placebo and raloxifene and 0-4 subjects (0-4%) in the combination product groups.

Mean Change from Baseline

Estrogen therapy has been associated with elevation of HDL cholesterol and triglycerides. In this study, combined bazedoxifene/conjugated estrogen and raloxifene were associated with mild mean decreases in total cholesterol from Baseline to Month

24 (cholesterol -9 to -14 mg/dL for combination drug, -7 mg/dL for raloxifene against placebo). Slight increases in triglycerides were noted (1 to 19 mg/dL for the active treatment groups against placebo). These changes are not likely to be clinically significant.

Bazedoxifene monotherapy has been associated with elevated transaminases. In this study, ALT and AST in active treatment groups were essentially unchanged compared to placebo. Alkaline phosphatase was reduced 12 to 16 U/L with active treatment compared to placebo, probably due to antiresorptive bone effect. Total bilirubin showed a statistically but probably not clinically significant reduction of -0.1 mg/dL in all treatment groups.

Bazedoxifene/conjugated estrogen and raloxifene were associated with slight mean decreases from Baseline to Month 24 in calcium (-0.1 to -0.2 mg/dL for active drug, no change for placebo) and phosphate (-0.2 to -0.3 mg/dL for active drug, no change for placebo).

No mean change from Baseline to Month 24 was noted for creatinine. No clinically significant change was noted for BUN.

Both bazedoxifene/conjugated estrogen and raloxifene were associated with slight mean decreases in hemoglobin and hematocrit from Baseline to Month 24 (hemoglobin, -0.1 to -0.2 g/dL; hematocrit, -0.5 to 0.7% for the combination drug, -0.3% for raloxifene). These changes are not clinically significant.

Shifts

Shift tables for laboratory were not provided.

Metabolic Substudy

Cholesterol and triglycerides were checked in all subjects with the chemistry panel at Screening, every 3 months during the first year of the study, and every 6 months during the second year. HDL and LDL cholesterol were checked yearly. Lipid parameters including cholesterol, HDL, LDL, and VLDL cholesterol, triglycerides, VLDL triglycerides, HDL2 and HDL3 cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein (a) were checked at Screening, Baseline, and every 6 months in the Osteoporosis Prevention II and Metabolic Substudy. This substudy consisted of about 25% of the population and was 1 to 5 years postmenopausal with one additional risk factor for osteoporosis.

Total cholesterol levels decreased at 24 months by 2 to 4% in the BZA/CE groups, 3% with raloxifene, and were not changed with placebo. This small change may not be significant.

HDL cholesterol levels increased at 24 months by 10 to 11% in the BZA/CE groups, 5% with raloxifene, and 1% with placebo. Estrogen therapy has been associated with elevation of HDL cholesterol.

LDL cholesterol levels decreased at 24 months by 7 to 11% in the BZA/CE groups, 6% with raloxifene, and were not changed with placebo.

VLDL cholesterol levels increased at 24 months by 9 to 31% in the BZA/CE groups, 14% with raloxifene, and 9% with placebo. This change may not be significant.

Triglyceride levels increased at 24 months by 12 to 25% in the BZA/CE groups, 7% with raloxifene, and 6% with placebo. Estrogen therapy has been associated with elevation of triglycerides.

VLDL triglyceride levels increased at 24 months by 13 to 28% in the BZA/CE groups, 6% with raloxifene, and 8% with placebo. This change may not be significant.

HDL2 cholesterol (protective against ischemic heart disease) levels increased at 24 months by 18 to 33% in the BZA/CE groups, 11% with raloxifene, and decreased 4% with placebo.

HDL3 cholesterol (may be protective against ischemic heart disease) levels increased at 24 months by 5 to 8% in the BZA/CE groups, 4% with raloxifene, and 3% with placebo. This small change may not be significant.

Apolipoprotein A1 (associated with HDL cholesterol) levels increased at 24 months by 9 to 11% in the BZA/CE groups, 6% with raloxifene, and 1% with placebo.

Apolipoprotein B (associated with chylomicrons and LDL cholesterol) levels changed at 24 months by -2 to 1% in the BZA/CE groups, was not changed with raloxifene, and increased by 4% with placebo.

Lipoprotein (a) is associated with an LDL-like particle and is a risk factor for atherosclerotic disease. Lipoprotein (a) levels decreased at 24 months by 17 to 21% in the BZA/CE groups, 15% with raloxifene, and 8% with placebo.

The effect of the lipid profile on arthrosclerosis would be expected to improve with BZA/CE based on HDL cholesterol level increase, LDL cholesterol level decrease, apolipoprotein A1 level increase, and lipoprotein (a) level decrease. Triglyceride level increase may have a deleterious effect.

Coagulation Parameters

The coagulation parameters prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III activity, protein C activity, protein S activity, plasminogen activity,

plasminogen activator inhibitor-1 activity, plasminogen activator inhibitor-1 antigen, and D-dimer were checked at Screening, Baseline, and every 6 months as part of the Osteoporosis Prevention II Substudy, about 25% of the population. This is the same population as in the metabolic study above.

Prothrombin time changed at 24 months by -0.18 to 0.31 (units not given) in the BZA/CE groups, 0.09 with raloxifene, and -0.05 with placebo. This is not a significantly different.

PTT changed at 24 months by -0.69 to 0.15 (units not given) in the BZA/CE groups, -0.50 with raloxifene, and -1.38 with placebo. This is not a significantly different.

Fibrinogen decreased at 24 months by 0.38 to 0.50 (units not given) in the BZA/CE groups, 0.36 with raloxifene, and increased 0.01 with placebo.

Antithrombin III activity decreased at 24 months by 27 to 29% in the BZA/CE groups, 26% with raloxifene, and 22% with placebo.

Protein C activity increased at 24 months by 0.01 to 0.06 (units not given) in the BZA/CE groups, decreased 0.01 with raloxifene, and increased 0.03 with placebo. This is not a significantly different.

Protein S activity increased at 24 months by 0.02 to 0.09 (units not given) in the BZA/CE groups, 0.11 with raloxifene, and 0.16 with placebo.

Plasminogen activity increased at 24 months by 0.07 to 0.11 (units not given) in the BZA/CE groups, 0.05 with raloxifene, and 0.07 with placebo. There may be a borderline difference between BZA/CE and placebo.

Plasminogen activator inhibitor-1 activity decreased at 24 months by 1.3 to 3.1 (units not given) in the BZA/CE groups, 1.1 with raloxifene, and increased 1.2 with placebo.

Plasminogen activator inhibitor-1 antigen decreased at 24 months by 0.9 to 6.6 (units not given) in the BZA/CE groups, 0.5 with raloxifene, and increased 2.0 with placebo. This is not a significantly different.

D-dimer activity changed at 24 months by -31 to 59 (units not given) in the BZA/CE groups, 65 with raloxifene, and 36 with placebo. This is not a significantly different.

There are not significant changes associated with taking BZA/CE on PT, PTT, protein C, plasminogen activator inhibitor-1 antigen, and D-dimer. Remaining factors affecting fibrinolysis (i.e. plasminogen activity, plasminogen activator inhibitor 1activity) change in a way which would enhance clot resolution. Fibrinogen, a procoagulant factor, was decreased in all BZA/CE treatment groups. The small differences in antithrombin III and

Protein S between the BZA/CE groups and placebo are unlikely to be clinically meaningful.

Electrocardiograms

ECGs were performed at Screening and Month 24 or early termination. ECG values of potential clinical importance occurring during the study were defined as:

- Heart rate increase of ≥15 beats/min and ≥120 beats/min
- Heart rate decrease of ≥15 beats/min and ≤50 beats/min
- PR interval ≥200 msec
- QT interval ≥480 msec
- QTc > 470 msec (females) or increase of ≥60 msec
- QRS interval ≥120 msec
- Rhythm any rhythm other than sinus rhythm
- Overall evaluation any evaluation other than normal

ECG results of potential clinical importance developing during the study are shown in Table 140. The total and most events are balanced between groups. The event QT interval ≥480 msec occurred in more subjects in the raloxifene group (6 subjects, 2%) and most BZA/CE groups (1-8 subjects, <1-3%) compared to placebo (1 subject, <1%), but this was not maintained with the QTc > 470 msec (females) or increase of ≥60 msec event (active treatment groups 9-18 subjects, 3-6%, placebo 10 subjects, 4%).

Table 140: Trial 303 ECG Results of Potential Clinical Importance Developing during

Event	BZA10/ CE0.625	BZA20/ CE0.625	BZA40/ CE0.625	BZA10/ CE0.45	BZA20/ CE0.45	BZA40/ CE0.45	Ralox	Plcbo	P-value[1]
	N=284[2]	N=274[2]	N=275[2]	N=287[2]	N=292[2]	N=278[2]	N=271[2]	N=267[2]	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
Total	100(35)	86(31)	82(30)	99(34)	116(40)	90(32)	102(38)	92(34)	0.240
HR increase	0	0	0	0	0	0	0	0	
HR decrease	2 (1)	0	1 (<1)	2 (1)	3 (1)	1 (<1)	2 (1)	4 (1)	0.547
PR ≥200 ms	12 (4)	9 (3)	10 (4)	10(3)	19 (7)	13 (5)	12 (4)	11 (4)	0.668
QT ≥480 ms	6 (2)	8 (3)	1 (<1)	3 (1)	5 (2)	2 (1)	6 (2)	1 (<1)	0.094
QTc > 470 ms or increase ≥60 ms	15 (5)	10 (4)	10 (4)	18 (6)	13 (4)	9 (3)	16 (6)	10 (4)	0.532
QRS ≥120 ms	8 (3)	4 (1)	7 (3)	4 (1)	11 (4)	6 (2)	6 (2)	4 (2)	0.541
Not sinus rhythm	5 (2)	3 (1)	2 (1)	3 (1)	3 (1)	4 (1)	1 (<1)	2 (1)	0.829
Not normal	80 (28)	70 (26)	64 (23)	77 (27)	90 (31)	73 (26)	80 (30)	76 (28)	0.584

Source: Clinical Study Report 64104, Table 10-44
1 P-value for Chi-square
2 N for the denominator may be slightly less than shown for certain measures (never more than 3 less)

Vital Signs

A total of 329 subjects were reported as having AEs of hypertension during the study: 47 subjects (11%) in the BZA 10 mg/CE 0.625 mg group, 42 subjects (10%) in the BZA 20 mg/CE 0.625 mg group, 39 subjects (9%) in the BZA 40 mg/CE 0.625 mg group, 49 subjects (11%) in the BZA 10 mg/CE 0.45 mg group, 45 subjects (10%) in the BZA 20

mg/CE 0.45 mg group, 34 subjects (8%) in the BZA 40 mg/CE 0.45 mg, 31 subjects (7%) in the raloxifene group, and 42 subjects (10%) in placebo). A total of 52 subjects were reported as having AEs of hypertensive crisis during the study: 6 subjects (1%) in the BZA 10 mg/CE 0.625 mg group, 8 subjects (2%) in the BZA 20 mg/CE 0.625 mg group, 4 subjects (1%) in the BZA 40 mg/CE 0.625 mg group, 7 subjects (2%) in the BZA 10 mg/CE 0.45 mg group, 9 subjects (2%) in the BZA 20 mg/CE 0.45 mg group, 6 subjects (1%) in the BZA 40 mg/CE 0.45 mg, 5 subjects (1%) in the raloxifene group, and 7 subjects (2%) in placebo). Estrogens have been reported to increase blood pressure in some patients, but that is not apparent for hypertension as an adverse event.

A potentially clinically important increase from baseline of systolic BP was defined as ≥ 20 mm Hg increase with absolute value of ≥ 160 mm Hg. This occurred on-therapy in 235 subjects; 25 subjects (6%) in the BZA 10 mg/CE 0.625 mg group, 32 subjects (8%) in the BZA 20 mg/CE 0.625 mg group, 36 subjects (9%) in the BZA 40 mg/CE 0.625 mg group, 31 subjects (8%) in the BZA 10 mg/CE 0.45 mg group, 26 subjects (6%) in the BZA 20 mg/CE 0.45 mg group, 31 subjects (8%) in the BZA 40 mg/CE 0.45 mg, 34 subjects (9%) in the raloxifene group, and 20 subjects (5%) in placebo. A clinically important increase from baseline of diastolic BP was defined as ≥ 15 mm Hg increase with absolute value ≥ 90 mm Hg. This occurred on-therapy in 347 subjects; 46 subjects (11%) in the BZA 10 mg/CE 0.625 mg group, 43 subjects (11%) in the BZA 20 mg/CE 0.625 mg group, 42 subjects (11%) in the BZA 40 mg/CE 0.625 mg group, 41 subjects (10%) in the BZA 10 mg/CE 0.45 mg group, 43 subjects (11%) in the BZA 20 mg/CE 0.45 mg group, 46 subjects (12%) in the BZA 40 mg/CE 0.45 mg, 43 subjects (11%) in the raloxifene group, and 43 subjects (%) in placebo. Not all subjects with potentially clinically important increases of blood pressure were reported as adverse events.

Mean change in systolic and diastolic blood pressure over the 24 months of the study was small and not different from placebo. Systolic blood pressure changed by a mean of 0.0 to 2.1 mmHg in the BZA/CE treatment groups compared to placebo with 0.8 mmHg change in the raloxifene treatment group. Diastolic blood pressure changed by a mean of -0.5 to 0.9 mmHg in the BZA/CE treatment groups compared to placebo with -0.6 mmHg change in the raloxifene treatment group.

Significant blood pressure increase was not seen with the bazedoxifene/conjugated estrogen in this study.

Weight increased was reported as an adverse event in 20 to 27 subjects (5-6%) in the BZA /CE treatment groups, 27 subjects (6%) in the raloxifene treatment group, and 21 subjects (5%) in the placebo group. A potentially clinically important weight gain of ≥ 15% and ≥ 25 pounds over the course of the study was reported in 1 to 7 subjects (<1-2%) in the BZA /CE treatment groups, 5 subjects (5%) in the raloxifene treatment group, and 4 subjects (1%) in the placebo group. Weight changed by a mean compared to placebo of -0.45 to 0.17 kg in the BZA /CE treatment groups and 0.29 kg in the

raloxifene treatment group. No significant weight change was noted with the BZA/CE combination.

Safety Conclusions

For combination bazedoxifene/conjugated estrogen the BZA 20 and 40 mg with either CE 0.45 mg or 0.625 mg doses were all well tolerated in this two year study in postmenopausal women. The BZA 10 mg/CE 0.45 mg and BZA 10 mg/CE 0.625 mg were not well tolerated due to endometrial and uterine safety issues. See also Dr. Gerald Willett's uterine safety review. The BZA 20mg/CE 0.625 mg and BZA 20 mg/CE 0.45 mg doses are the doses for which registration is being sought.

Adverse event rates, deaths, serious adverse event rates, and withdrawal for adverse events were balanced across treatment groups. Deaths were few (6 total) and without concerning pattern.

Serious adverse events occurred in about 7% of the study population. An imbalance of SAEs was noted in the SOC cardiac disorders, with more subjects in the CE 0.625 mg treatment groups reporting SAEs (4 subjects (1%) in the BZA 10 mg/CE 0.625 mg group, 3 subjects (1%) in the BZA 20 mg/CE 0.625 mg group, and 3 subjects (1%) in the BZA 40 mg/CE 0.625 mg group; no more than 1 subject in any other group). In the BZA 10 mg/CE 0.625 mg group, all 4 subjects reported coronary artery disease. In the BZA 20 mg/CE 0.625 mg group, one subject reported CAD and 1 reported myocardial infarction. Women's Health Initiative Studies showed increased risk of non-fatal myocardial infarction with estrogen plus progesterone but not with estrogen alone. This should be compared to other clinical studies, but may be a chance occurrence as the increase was not noted in the CE 0.45 mg treatment groups. An imbalance in CVA and TIA related SAEs is discussed in cerebrovascular events below.

Withdrawals for adverse events occurred in about 13% of the study population. An imbalance in withdrawals for CAD is discussed in SAEs above. More subjects (6, no more than 2 in any other group) withdrew from the placebo group for osteoporosis, likely as that group lacked treatment with a bone protective agent. The Reproductive System and Breast SOC showed a marked imbalance in withdrawals with increase in the BZA 10 mg/CE 0.625 treatment group (23 subjects, no more than 9 in any other group. This was primarily from an increase in endometrial hyperplasia and vaginal hemorrhage. These findings likely resulted from a lack of uterine protective effect of BZA 10 mg. Vascular SOC withdrawals appear driven by hot flush withdrawals, which occurred primarily with raloxifene (16 subjects) and placebo (12 subjects), although 8 subjects also withdrew in the BZA 40 mg/CE 0.45 group. Given the population, hot flushes with placebo and raloxifene are not surprising. It appears the higher dose of bazedoxifene combined with the lower dose of conjugated estrogen may not have as great a tendency to reduce hot flushes as other active dose combinations tested.

Venous thromboembolism is a concern with conjugated estrogens and also with bazedoxifene monotherapy. Venous thromboembolism is not seen with the combination BZA/CE in this study more than placebo, particularly at the doses considered for registration. Of note, venous thromboembolism is also a concern for raloxifene, an approved active comparator also used in the study. No excess of VTE events were reported in this study with raloxifene, which raises concerns for underreporting of VTE events for the combination product as well.

Cerebrovascular events have been a concern both with estrogens and bazedoxifene monotherapy. Considered in total, there remains a slight concern with the BZA/CE combination therapy. If only the more definite preferred terms of cerebral hemorrhage, cerebral infarction, CVA, and TIA are considered, 3 events were reported in the BZA 10 mg/CE 0.625 mg group, no events in the BZA 20 mg/CE 0.625 mg group, 2 events in the BZA 40 mg/CE 0.625 mg group, 1 event in the BZA 10 mg/CE 0.45 mg group, 1 event in the BZA 20 mg/CE 0.45 mg group, 1 event in the BZA 40 mg/CE 0.45 mg group, and no events with either raloxifene or placebo. Raloxifene, an agent known to induce stroke, had only 3 episodes of syncope reported for cerebrovascular events in this study. Stroke reports for all treatment groups were below that expected based on the WHI study.

The Neoplasm SOC is balanced between treatment groups. For preferred terms, overall little difference is noted between treatment groups. Breast cancer was reported in a subject in the BZA 40 mg/CE 0.625 mg group, 2 subjects in the BZA 10 mg/CE 0.45 mg group, a subject in the BZA 20 mg/CE 0.45 mg group, an a subject on placebo. A single case of endometrial cancer was reported in the BZA 20 mg/CE 0.45 mg group and a uterine neoplasm in the BZA 10 mg/CE 0.45 mg group. A case of ovarian cancer was reported in the BZA 40 mg/CE 0.625 mg group and a case of ovarian epithelial cancer in the BZA 10 mg/CE 0.45 mg group.

Breast adverse events appear generally balanced between treatment groups. Fibrocystic breast disease may be slightly more common in the BZA/CE groups (0 to 3 subjects, 0-1%, no subjects with raloxifene or placebo). This will be further compared to in other clinical studies.

The Reproductive System and Breast Disorder SOC showed increased events in the bazedoxifene 10 mg treatment groups (BZA 10 mg/CE 0.625 mg group 155 subjects (36%), BZA 10 mg/CE 0.45 mg group 143 subjects (33%), other active treatment groups 89 to 118 subjects (21-27%), placebo 114 subjects (27%)). Particularly contributing to this difference were vaginal hemorrhage, endometrial hyperplasia, vaginal discharge, and genital discharge. Vulvovaginal pruritis was increased in these groups and in the raloxifene group. These findings were largely consistent with a lack of uterine protective effect with bazedoxifene 10 mg.

Uterine polyps were more common in all conjugated estrogen treatment groups except the BZA 40 mg/CE 0.45 mg group (BZA 40 mg/CE 0.45 mg group 2 subjects (<1%), other CE groups 4-11 subjects (1-3%), Raloxifene no subjects, placebo 2 subjects (<1%)). Uterine polyps have been associated with estrogen use.

The preferred term vulvovaginal candidiasis predominated in the BZA 10 mg/CE 0.625 mg group and BZA 20 mg/CE 0.625 mg group. A similar pattern but fewer subjects are seen with the preferred terms vulvovaginal mycotic infection, vulvovaginitis, and candidiasis. As conjugated estrogen is associated with vaginal candidiasis, this finding is not surprising. It appears increasing doses of bazedoxifene may be associated with less candidiasis.

Ultrasound uterus abnormal was reported most commonly in the bazedoxifene 10 with conjugated estrogen groups. This is consistent with lack of uterine protection with 10 mg bazedoxifene.

See Section 6.4 of NDA review for uterine safety analysis.

The preferred term muscle spasm was lower in the placebo group. As muscle spasms have been reported with both conjugated estrogens and raloxifene, this finding is not surprising.

Alopecia may be associated with the combination product. Alopecia has been associated with estrogen use.

There may be a slight increase in urticaria with the combination product. This will be further compared with other clinical studies.

Hot flushes, not surprisingly, may be more frequent in the raloxifene and placebo groups.

The preferred terms aspartate aminotransferase increased and alanine aminotransferase increased were reported more often in the raloxifene group. There did not appear to be a tendency for these preferred terms to be more common with the combination product. Bazedoxifene monotherapy has been associated with increased transaminases, but that is not noted in this study.

In the metabolic substudy, the effect of BZA/CE compared to placebo on HDL cholesterol level showed about a 10% increase and on LDL cholesterol level about a 9% decrease. Triglyceride levels increased by about 13%. Total cholesterol levels were little changed. Similar changes are noted with conjugated estrogens. The overall net effect on lipid profile was probably about neutral. In the same substudy, effects on coagulation factors were probably overall neutral.

Trial 3307

Protocol 3115A1-3307-WW: A double blind, randomized, placebo- and active controlled efficacy and safety study of the effects of bazedoxifene/conjugated estrogen combinations on endometrial hyperplasia and prevention of osteoporosis in postmenopausal women.

Of the 1886 subjects randomized, 43 were not treated. The remaining 1843 subjects who received at least one dose of study drug constitute the safety population. Safety endpoints were analyzed according to the treatment actually received.

Events Rates:

About 90% of trial 3307 subjects in each treatment group experienced at least one adverse event following initial screening visit. Treatment-emergent AEs were reported in 82.7% of placebo subjects and 84.3-85.2% of subjects in the active treatment groups (see Table 141 below). SAE incidence was similar in the two CE/BZA groups and the placebo group (3.6-3.8%), and slightly higher in the CE/MPA group (5.9%). Discontinuations due to AEs were also more frequent in the CE/MPA group (14.1%, vs. 7.0-7.6% in the other groups). There was one death in the placebo group.

Table 141: Trial 3307: Subject incidence (n,%) of adverse event classes

	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Any treatment emergent* AE	375 (84.3)	404 (85.2)	194 (84.3)	187 (85.0)	392 (82.7)
Serious adverse events	16 (3.6)	17 (3.6)	5 (2.2)	13 (5.9)	18 (3.8)
Deaths	0	0	0	0	1 (0.2%)
Withdrawal due to AE	34 (7.6)	33 (7.0)	16 (7.0)	31 (14.1)	33 (7.0)

* Treatment emergent defined as AEs occurring after first dose and before last dose of study drug
Source: CSR Table 10-1

Exposure:

Over 80% of CE/BZA subjects completed the one year trial, and total exposure to CE/BZA (both doses) was 797 subject years (Table 142).

Table 142: Trial 3307: Percent of subjects completing 28 or 48 weeks of treatment

	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
≥ 28 weeks	85	88	84	79	85
≥ 48 weeks	80	83	81	72	81
Source: Supportive Table 15.48, CSR, p. 969/2153					

Compliance was at least 93% in all treatment arms.

Deaths:

There was one death: subject #703367, a 53 year-old woman assigned to placebo with no relevant medical history except smoking, and no prior or concomitant medications. She was reportedly found dead by her husband on trial day 207; no autopsy was performed. The verbatim on the death certificate was arteriosclerosis coronary artery.

Serious Adverse Events:

There were 69 subjects who experienced a total of 96 SAEs. The incidence was higher in the CE/MPA group (5.9%) than the other groups (2.2-3.8%). SOC classes with the most subjects with SAEs were neoplasms (n=24); infections/infestations (n=7); injury, poisoning and procedural complications (n=6). SAEs considered treatment related (all discussed below) included CVA (1), DVT (1), breast cancer (3), migraine (1), and cholecystitis (2). See Table 143.

Table 143: Trial 3307: Serious adverse events on therapy or post therapy, by SOC

System organ class	**CE 0.45mg BZA 20 mg** N=445		**CE 0.625mg BZA 20 mg** N=474		**BZA 20 mg** N=230		**CE 0.45 mg MPA 1.5mg** N=220		**Placebo** N=474	
	# subjects	#events	# subjects	#events	# subjects	#events	# subjects	#events	# subjects	#events
Any SAE	16 (3.6%)	22	17 (3.6%)	27	5 (2.2%)	7	13 (5.9%)	27	18 (3.8%)	24
Discontinuation due to SAE	1 (0.2%)		5 (1.1%)		2 (0.9%)		4 (1.8%)		1 (0.2%)	
SAE considered treatment related	1 (0.2%)		2 (0.4%)		0		3 (1.4%)		2 (0.4%)	
Neoplasms	7	11	3	4	2	2	6	13	6	10
Gastrointestinal	1	1	2	6	1	1	0	0	1	1
Injury, poisoning	1	2	2	2	0	0	1	2	2	2
Infections	1	1	2	2	1	1	0	0	3	3
Musculoskeletal	2	2	1	1	0	0	1	2	0	0
Cardiac	1	1	1	1	0	0	0	0	3	3
General disorders	1	1	0	0	1	1	2	2	1	1
Nervous system	0	0	2	2	0	0	1	1	1	1

System organ class	CE 0.45mg BZA 20 mg N=445		CE 0.625mg BZA 20 mg N=474		BZA 20 mg N=230		CE 0.45 mg MPA 1.5mg N=220		Placebo N=474	
	# subjects	#events	# subjects	#events	# subjects	#events	# subjects	#events	# subjects	#events
Ear, labyrinth	1	1	1	1	0	0	0	0	1	1
Hepatobiliary.	0	0	1	1	0	0	1	1	1	1
Psychiatric	0	0	1	2	0	0	0	0	1	1
Vascular	1	1	0	0	0	0	2	2	0	0
Congenital	0	0	1	2	0	0	0	0	0	0
Endocrine	0	0	0	0	0	0	1	2	0	0
Metabolism	0	0	0	0	1	1	1	1	0	0
Investigations	0	0	1	2	0	0	0	0	0	0
Blood/lymphatic	0	0	0	0	0	0	1	1	0	0
Renal/urinary	0	0	1	1	0	0	0	0	0	0
Respiratory	1	1	0	0	0	0	0	0	0	0
Skin, SC tissue	0	0	0	0	1	1	0	0	0	0

*Includes SAEs occurring during treatment period and up to 30 days post last dose
Source: AEMEDDRA dataset (re-coded to v. 15.1 submitted on 11/30/12, #0007)
Similar table in CSR table 15.54 p. 1701/2153 (based on MedDRA 13.1)

Adverse Events Leading to Withdrawal:

The CE/MPA treatment group had the highest rate of discontinuations due to adverse events at 14.1%, vs. 7.0-7.6% for the other groups, contributing to the higher number of overall dropouts from this arm. The imbalance was related to an excess of gynecologic and breast disorders in this CE/MPA group, particularly the PTs of breast tenderness, pelvic pain and vaginal hemorrhage (see Table 144 and Table 145 below). Conversely, the PT of hot flush was associated with discontinuations in the other treatment groups but not in the CE/MPA group.

In comparing CE/BZA to placebo, there were numerically more discontinuations with CE/BZA in 3 SOC classes:

- GI disorders, attributable to a variety of complaints, including dyspepsia, abdominal distention and nausea
- Investigations, attributable primarily to 3 subjects each in CE.45/BZA and CE.625/BZA groups, and none in placebo, with discontinuations due to abnormal LFTs (see below)
- Vascular disorders, mostly related to more discontinuations due to flushing with CE/BZA than with placebo

There were 13 discontinuations due to an SAE; these were mostly for conditions considered unrelated to the study drug. The exceptions were two CE 0.625/BZA subjects (CVA; migraine with aura) and one CE/MPA subject (DVT).

Table 144: Trial 3307: Subjects withdrawing (n,%) due to Adverse Events (most frequent SOC classes)

System Organ Class Preferred Term	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Discontinued due to any AE	34 (7.6)	33 (7.0)	16 (7.0)	**31 (14.1)**	33 (7.0)
Discontinued due to any SAE	1 (0.2)	5 (1.1)	2 (0.9)	**4 (1.8)**	1 (0.2)
Gastrointestinal disorders	**8 (1.8)**	**7 (1.5)**	2 (0.9)	1 (0.5)	**2 (0.4)**
Investigations	**6 (1.3)**	**7 (1.5)**	0	2 (0.9)	**2 (0.4)**
Musculoskeletal and connective tissue disorders	2 (0.4)	3 (0.6)	2 (0.9)	1 (0.5)	5 (1.1)
Nervous system disorders	1 (0.2)	7 (1.5)	2 (0.9)	2 (0.9)	4 (0.8)
Psychiatric disorders	4 (0.9)	5 (1.1)	1 (0.4)	2 (0.9)	4 (0.8)
Reproductive system and breast disorders	2 (0.4)	4 (0.8)	2 (0.9)	**15 (6.8)**	8 (1.7)
Skin and subcutaneous tissue disorders	3 (0.7)	2 (0.4)	2 (0.9)	3 (1.4)	4 (0.8)
Vascular disorders	**9 (0.2)**	**4 (0.8)**	3 (1.3)	3 (1.4)	**2 (0.4)**

Source: Table AE5_W_151_1%

Table 145: Trial 3307: Subjects withdrawing (n,%) due to Adverse Events (most frequent preferred terms)

System Organ Class Preferred Term	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
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)
Hot flush	6 (1.3)	3 (0.6)	3 (1.3)	**0**	2 (0.4)

Source: Table AE5_W_151_1%

Adverse Events

AEs occurring during either the 52-week treatment period or the 2-week post-treatment period were reported by 86-88% of subjects in each treatment arm. Table 146 below lists all AE SOCs, and all PTs occurring in ≥5% of subjects. The most commonly

occurring AEs by System Organ Class were infections and infestations (45.4% of overall subjects), musculoskeletal and connective tissue disorders (37.3%), gastrointestinal disorders (31.7%) and nervous system disorders (30.6%). Disorders in these SOCs were generally distributed evenly between treatment groups, except that the placebo group tended to have slightly fewer GI AEs. The most commonly occurring AEs by preferred term were headache (20.9% of overall subjects), nasopharyngitis (14.8%), back pain (11.3%), pain in extremity (9.1%), and arthralgia (8.8%).

The most pronounced treatment group imbalances were in the SOC reproductive and breast disorders (37% of CE/MPA subjects vs. 16-20% of subjects in the other arms). This was mainly due to significant excess of both breast tenderness and vaginal hemorrhage in the CE/MPA group relative to the other 4 groups (overall p<.001 for each).

Reviewer comment: The imbalances in breast tenderness and vaginal hemorrhage are consistent with the daily diary reports of these symptoms which were significantly more frequent in CE/MPA subjects compared with the other groups, as noted in the efficacy section above.

Other AE SOCs with imbalances were neoplasms benign and malignant with 6.4% of CE/MPA subjects vs. 2.1-2.7% in other groups; and skin and subcutaneous tissue disorders (10% of placebo subjects, vs. 13-18% in other groups). In neither of these SOCs however was there an imbalance of specific AEs (see below for discussion of neoplasms).

The PT Hot flush was significantly less frequent during the treatment period in the CE/MPA group (0.9% of subjects) compared to the CE/BZA groups (2.5-3.1%), BZA group (6.1%) or placebo (5.9%).

Reviewer comment: BZA appears to impair the effect of estrogen in relieving flushing symptoms. It is unclear whether CE/BZA has any benefit over placebo in this regard, because although the incidence of flushing was lower with CE/BZA than placebo, the discontinuation rate attributed to flushing was higher, as noted above. (Note: imbalances are less apparent in the table below because it includes events occurring in the follow-up period, when flushing occurred due to discontinuation of estrogens.)

AEs of muscle spasm, consistent with previous CE/BZA and BZA studies, were numerically more frequent among CE/BZA and BZA subjects (8.0-9.6%) compared with CE/MPA (5.9%) or placebo (6.1%). Nasopharyngitis was also more frequent in the BZA and CE/BZA groups (13.3-19.3%) compared with CE/MPA (12.3%) or placebo (11.6%) (overall p=0.005). Oropharyngeal pain, in contrast, was significantly more frequent with CE/MPA (9.1%) relative to the BZA and CE/BZA groups (4.5-4.8%) or placebo (2.7%) (overall p=0.008).

Table 146: Trial 3307: Subject incidence (n,%) of adverse events† by SOC class, with preferred terms reported in ≥5% of subjects

System Organ Class Preferred Term	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Any AEs	391 (88)	414 (87)	198 (86)	192 (87)	408 (86)
Blood and lymphatic disorders	2 (0.4)	6 (1.3)	3 (1.3)	7 (3.2)	7 (1.5)
Cardiac disorders	8 (1.8)	9 (1.9)	1 (0.4)	5 (2.3)	6 (1.3)
Congenital, familial, genetic	0 (0)	1 (0.2)	0 (0)	0 (0)	1 (0.2)
Ear and labyrinth disorders	15 (3.4)	14 (3.0)	6 (2.6)	6 (2.7)	8 (1.7)
Endocrine disorders	4 (0.9)	4 (0.8)	0 (0)	2 (0.9)	4 (0.8)
Eye disorders	12 (2.7)	19 (4.0)	4 (1.7)	5 (2.3)	12 (2.5)
Gastrointestinal disorders	157 (35)	154 (33)	73 (32)	69 (31)	132 (28)
Abdominal pain	15 (3.4)	26 (5.5)	11 (4.8)	11 (5.0)	23 (4.9)
Constipation	19 (4.3)	20 (4.2)	14 (6.1)	13 (5.9)	17 (3.6)
Diarrhea	30 (6.7)	24 (5.1)	10 (4.3)	11 (5.0)	21 (4.4)
Dyspepsia	24 (5.4)	13 (2.7)	8 (3.5)	11 (5.0)	10 (2.1)
Nausea	31 (7.0)	25 (5.3)	8 (3.5)	11 (5.0)	25 (5.3)
General disorders	62 (14)	77 (16)	34 (15)	28 (13)	65 (14)
Pain	18 (4.0)	23 (4.9)	14 (6.1)	6 (2.7)	20 (4.2)
Hepatobiliary disorders	5 (1.1)	3 (0.6)	2 (0.9)	3 (1.4)	3 (0.6)
Immune system disorders	15 (3.4)	18 (3.8)	6 (2.6)	8 (3.6)	16 (3.4)
Infections and infestations	217 (49)	2123 (45)	99 (43)	98 (45)	210 (44)
Influenza	23 (5.2)	24 (5.1)	17 (7.4)	11 (5.0)	20 (4.2)
Nasopharyngitis	**86 (19)**	**63 (13)**	**41 (18)**	**27 (12)**	**55 (12)**
Sinusitis	39 (8.8)	35 (7.4)	15 (6.5)	12 (5.5)	31 (6.5)
Upper respiratory tract inf.	33 (7.4)	36 (7.6)	8 (3.5)	10 (4.5)	27 (5.7)
Urinary tract infection	26 (5.8)	15 (3.2)	12 (5.2)	5 (2.3)	28 (5.9)
Injury, poisoning, procedural	62 (14)	62 (13)	34 (15)	37 (17)	78 (17)
Procedural pain	15 (3.4)	21 (4.4)	2 (0.9)	13 (5.9)	16 (3.4)
Investigations	45 (10)	47 (9.9)	22 (9.6)	30 (14)	54 (11)
Metabolism and nutrition	18 (4.0)	9 (1.9)	12 (5.2)	10 (4.5)	16 (3.4)
Musculoskeletal and connective tissue disorders	163 (37)	189 (40)	84 (37)	76 (35)	177 (37)
Arthralgia	35 (7.9)	46 (9.7)	19 (8.3)	18 (8.2)	44 (9.3)
Back pain	45 (10)	61 (13)	26 (11)	19 (8.6)	57 (12)
Muscle spasms	**44 (9.9)**	**39 (8.2)**	**22 (9.6)**	**14 (6.4)**	**32 (6.8)**
Musculoskeletal pain	29 (6.5)	30 (6.3)	10 (4.3)	9 (4.1)	29 (6.1)
Myalgia	30 (6.7)	24 (5.1)	17 (7.4)	12 (5.5)	21 (4.4)
Pain in extremity	39 (8.8)	42 (8.9)	15 (6.5)	29 (13)	43 (9.1)
Neoplasms benign & malignant	**12 (2.7)**	**10 (2.1)**	**6 (2.6)**	**14 (6.4)**	**13 (2.7)**
Nervous system disorders	117 (26)	136 (29)	60 (26)	71 (32)	145 (31)
Headache	79 (18)	98 (21)	44 (19)	51 (23)	113 (24)
Psychiatric disorders	55 (12)	58 (12)	26 (11)	21 (9.5)	52 (11)
Insomnia	23 (5.2)	21 (4.4)	15 (6.5)	11 (5.0)	30 (6.3)
Renal and urinary disorders	13 (2.9)	17 (3.6)	8 (3.5)	6 (2.7)	20 (4.2)
Reproductive/ breast	**91 (20)**	**100 (21)**	**37 (16)**	**82 (37)**	**95 (20)**

System Organ Class Preferred Term	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
disorders					
Breast tenderness	**15 (3.4)**	**18 (3.8)**	**5 (2.2)**	**25 (11)**	**14 (3.0)**
Vaginal hemorrhage	**25 (5.6)**	**19 (4.0)**	**13 (5.7)**	**34 (16)**	**29 (6.1)**
Respiratory/ thoracic/ mediastinal	76 (17)	71 (15)	31 (14)	44 (20)	61 (13)
Cough	23 (5.2)	26 (5.5)	9 (3.9)	11 (5.0)	26 (5.5)
Oropharyngeal pain	**20 (4.5)**	**22 (4.6)**	**11 (4.8)**	**20 (9.1)**	**13 (2.7)**
Skin/ subcutaneous tissue	**57 (13)**	**71 (15)**	**33 (14)**	**40 (18)**	**47 (9.9)**
Social circumstances	0	1 (0.2)	1 (0.4)	0	0
Surgical/medical procedures	0	0	0	0	1 (0.2)
Vascular disorders	39 (8.8)	50 (11)	24 (10)	17 (7.7)	50 (11)
Hot flush	27 (6.1)	37 (7.8)	20 (8.7)	11 (5.0)	38 (8.0)

† All AEs occurring during treatment and post-treatment phases
Source: AEMEDDRA dataset and AE5_OTPT_151 table, both re-coded to MedDRA v. 15.1 and submitted on 11/30/12, #0007)

Adverse Events of Special Interest:

Because of the increased cardiovascular risk with estrogen + progestin combinations such as CE/MPA, standardized MedDRA queries (SMQ) of ischemic heart disease, CNS hemorrhage, cerebrovascular accidents, embolic and thrombotic events were conducted.

Venous thromboembolism (VTE)

During the trial there was one report of deep vein thrombosis (DVT), and no reports of pulmonary embolus or retinal vein thrombosis.

The subject with DVT (#706459) was a 51 y/o woman who presented on day 102 of treatment with CE/MPA, with pain and swelling of the R lower leg x 10 days and dyspnea. Ultrasound demonstrated DVT of popliteal and posterior tibial veins; chest CT showed no evidence of embolus. She was treated with anticoagulants and recovered; study drug was discontinued. Other than elevated BMI of 32.87 kg/m^2, no risk factors were noted.

There was also one report of phlebitis superficial in one CE 0.45/ BZA subject (#700106). This was a 58 y/o woman who reported leg cramps on day 5 of treatment, then localized swelling, warmth and tenderness adjacent to a varicose vein. A venous Doppler showed no evidence of DVT. She was treated with ibuprofen, the study drug was discontinued and symptoms resolved.

Reviewer comment: There were no VTE events in either CE/BZA group, constituting about 800 woman-years of exposure (~375 for 0.45 dose, ~425 for 0.625 dose). Using the "rule of 3", there is 95% confidence that the VTE incidences are no greater than approx. 80 events per 10,000 woman-years for CE

0.45/BZA, and 70 events per 10,000 woman-years for CE 0.625/BZA. If the two doses are pooled the VTE incidence could be zero to approx. 37.5 events per 10,000 woman-years in the population studied (with exclusion for prior VTE history). For comparison, women age 50-59 y/o in the WHI, some of whom had a prior history of VTE, had a VTE incidence of 19 per 10,000 woman years for CE 0.625 /MPA 2.5 (8 per 10,000 for placebo). Therefore the lack of VTE events in either CE/BZA group is reassuring but it remains unclear how the VTE risk of CE/BZA compares to CE/MPA.

Ischemic cardiac events

There were two subjects with SAEs of **myocardial infarction**, each with significant risk factors:

- Subject 704220 was a 51 y/o woman with risk factors of smoking, hyperlipidemia and a family history of CAD who was assigned to **CE 0.45/BZA**. On trial day 353 (4 days after last dose) she experienced chest pain; cardiac enzymes were elevated and she was diagnosed with **MI** and **coronary artery disease**. Heart catheterization showed moderate CAD and mild LV dysfunction. She recovered.
- Subject 703704 was also a 51 y/o woman and also had risk factors of smoking, dyslipidemia and a family history of CAD. She was assigned to **placebo** and on trial day 343 experienced chest pain, shortness of breath and had elevated cardiac enzymes. She was diagnosed with non Q wave **MI**. Catheterization showed single vessel disease. She recovered.

In addition there were 3 other cardiac SAEs:

- Subject 708173 was also a 51 y/o woman, with history of hypertension. She was assigned to **CE 0.625 mg/BZA** and stopped taking it on day 57 because of outpatient surgery. She developed chest pain 13 days later and was hospitalized. Cardiac workup including myocardial scintigraphy was negative and symptoms were attributed to her hypertension. She recovered. The event was coded as **angina pectoris**.
- Subject 703367, as noted above, was the only subject who died during the trial. She was a 53 y/o smoker assigned to **placebo** who died in her sleep without prior history; the death was attributed to **coronary artery arteriosclerosis** although no autopsy was done.
- Subject 700503 was a 56 y/o woman with past history of migraine headaches, mitral valve prolapse, anxiety disorder and hypothyroidism, who was assigned to **placebo**. She was hospitalized 3 times during the trial: on day 136 for chest and epigastric pain, nausea and vomiting, cardiac evaluation including heart cath negative, dx as anxiety disorder; on day 195 with acute cholecystitis leading to cholecystectomy; and on day 352 with palpitations and tachycardia, elevated TFTs and diagnosis of resolved **atrial fibrillation**.

Reviewer comment: It is unclear whether any of these 3 events were related to heart disease. Subject 708173 had hypertension but evaluation of chest pain

showed no evidence of CAD. Subject 700503 experienced atrial fibrillation which may have been related to excessive thyroid replacement.

Cerebrovascular events

One subject (#701907) experienced a **CVA** on day 83 of treatment with **CE 0.625/BZA**. This was a 54 y/o woman with hypertension, hyperlipidemia and family history of CVA (mother). She presented with transient slurred speech and L hand numbness/weakness. MRI revealed multiple acute R cerebral infarcts, normal Circle of Willis and vertebral arteries; carotid Doppler was unremarkable; TEE showed a patent foramen ovale. She was treated with anticoagulants (enoxaparin, warfarin, ASA) and withdrawn from the trial.

Another subject (#707158), a 62 y/o woman had an AE of **carotid artery stenosis**. She was noted to have bilateral carotid bruits at screening and was assigned to **CE 0.45/BZA**. Beginning on day 110, elective workup showed stenoses of multiple arteries including both carotids, R vertebral, L subclavian and L superficial femoral artery. Because of the findings she discontinued the trial. She was asymptomatic throughout and ECGs were normal.

A 44 y/o subject (#709882) treated with **CE.45/BZA** experienced an SAE. She had a history of headaches, and was hospitalized on trial day 80 with nausea, vertigo and headache. Carotid artery Doppler, cranial CT and MRI/MRA showed no specific abnormalities. Blood pressure was mildly elevated and was treated. Symptoms resolved. Study drug was stopped. The event was termed “circulatory failure in regions of vertebral and basilar arteries” and was not considered treatment related.

Reviewer comment: Subject 707158 had extensive vascular disease which is highly likely to have preceded the trial and therefore unlikely related to treatment. It is unclear if the event experienced by subject 709882 was cerebrovascular in nature.

Breast cancer

All women were required to have a normal screening/baseline mammogram (BI-RADS 1 or 2). During or immediately following the treatment period, 11 women had clinically important abnormal mammograms (BI-RADS 4 or 5), resulting in diagnosis of malignancy in 4 subjects and benign disease in 7 (6 of these underwent biopsy). See Table 147.

Table 147: Trial 3307: Subjects with abnormal mammograms (BI-RADS 4 or 5)

Diagnosis	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Invasive cancer	2	0	0	1	1
Benign disease	2	2	1	2	0

Four women (2 treated with CE 0.45/BZA, 1 with CE/MPA, 1 with placebo) were diagnosed with breast cancer:

- #702167: a 55 y/o woman with strong family history of breast Ca, assigned to **CE 0.45/BZA**. A final trial visit mammogram on day 357 was abnormal; subsequent mastectomy was performed with invasive Ca with lobular features, 1 cm tumor, ER 100% positive, sentinel nodes negative.
- #703671: a 56 y/o woman with h/o benign breast cysts (S/P bilat. biopsies) and strong family history of breast cancer, assigned to **CE 0.45/BZA**. On trial day 351, a new lesion was palpated leading to mastectomy and diagnosis of a 1.7 x 1.5 x1.5 cm tumor, invasive ductal Ca with 2/14 + axillary nodes, given chemotherapy.
- #703809: a 57 y/o woman with a family history of breast cancer and prior history of multiple breast biopsies, who had participated in two previous CE/BZA clinical trials. She was assigned to **CE/MPA**. On day 356, mammogram showed increased microcalcifications; positive biopsy resulted in mastectomy, dx infiltrating ductal Ca Grade II/III and DCIS, negative sentinel nodes.
- #706959: a 63 y/o woman with history of benign breast biopsies, no family history, assigned to **placebo**. Abnormal mammogram on trial day 353 with diagnosis of 0.5 cm tumor with invasive CA, no angiolymphatic invasion, ER+ 95%, breast conserving surgery, sentinel nodes negative.

Other breast related AEs

As noted above, breast tenderness was most frequent in the CE/MPA group. However, breast pain and the other breast related AEs listed in the table below were more evenly distributed. Unlike the subjects discussed above with abnormal mammograms resulting in biopsy, the subjects represented in Table 148 (e.g. mammogram abnormal, benign breast neoplasm, breast disorder and breast mass) had findings which did not require biopsy. Except for several subjects with breast tenderness, these conditions did not result in trial discontinuation.

Table 148: Trial 3307: Other breast AEs

Preferred term	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Breast tenderness	15	18	5	25	14
Breast pain	4	10	2	4	2
Mammogram abnormal	3	1	0	1	1
Benign breast neoplasm	0	0	1	0	0
Breast calcifications	0	0	0	1	1
Breast cyst	2	1	1	1	0
Breast disorder*	2	1	1	0	0
Breast mass	2	0	0	3	4
Breast enlargement	0	0	1	0	2

*verbatim terms include asymmetry, hypoechoic areas, sense of fullness
Source: CSR Table 10-10 and AEMEDDRA dataset

Neoplasms (other than breast)

As noted above, the CE/MPA group had a mild excess of subjects in the SOC neoplasms (benign and malignant) of 6.4% compared to 2.1% - 2.7% for the other groups. As shown in Table **Table**149 below, this is attributable to slightly greater numbers of CE/MPA subjects with AE of uterine leiomyoma (fibroid) and other benign neoplasms, and basal cell Ca. The CE/BZA groups were similar to placebo in incidence of various neoplasms. There were no uterine cancers or ovarian neoplasms in any treatment group. There was one benign Fallopian tube neoplasm in a BZA 20 mg subject: a 47 y/o woman who presented on day 108 with acute abdominal pain, with laparoscopic diagnosis and excision of the 11x5x5 mm benign tumor.

Table 149: Trial 3307: Subject incidence of neoplasms

Preferred term	**CE 0.45 BZA 20** N=445	**CE 0.625 BZA 20** N=474	**BZA 20** N=230	**CE 0.45 MPA 1.5** N=220	**Placebo** N=474
Any neoplasm	12 (2.7%)	10 (2.1%)	6 (2.6%)	14 (6.4%)	13 (2.7%)
Uterine leiomyoma	1	4	3	4	4
Other benign neoplasm	6	4	2	5	5
Any malignancy	7 (1.6%)	3 (0.6%)	1 (0.4%)	6 (2.7%)	6 (0.4%)
Basal cell carcinoma	2	1	1	3	1
Breast cancer Breast cancer metastatic Breast cancer stage II	2	0	0	1	1
Colon cancer stage IV Hepatic cancer metastatic Lung cancer metastatic Metastases to spine Metastatic pain (all the same subject)	0	0	0	1	0
Hodgkin's disease	0	0	0	0	1
Lung neoplasm	0	0	0	0	1
Malignant melanoma	2	1	0	0	1
Squamous cell Ca	1	0	0	1	0
Squamous cell Ca of skin	1	1	0	0	1
Source: AEMEDDRA dataset and AE5_OTPT_151 table submitted on 11/30/12, #0007					

Gynecologic bleeding

As noted above, daily diary assessments of bleeding or spotting showed that CE/MPA subjects were significantly less likely to have prolonged amenorrhea during therapy. This is also reflected in the AE reports, where AEs related to bleeding were much more commonly reported in the CE/MPA group (18.2%, vs. 2.5-5.2% in the other groups). See Table 150. None of the affected women required hospitalization, transfusion and/or "immediate medical attention", however 14 dropped out because of the bleeding and one CE/MPA subject (#705961) experienced a drop in Hct from 39.2 at baseline to 31.2.

Table 150: Trial 3307: Subject incidence of vaginal/uterine hemorrhage during therapy (TEAEs*)

Preferred term	CE 0.45mg BZA 20 mg N=445	CE 0.625mg BZA 20 mg N=474	BZA 20 mg N=230	CE 0.45 mg MPA 1.5mg N=220	Placebo N=474
Total	16 (3.6%)	12 (2.5%)	12 (5.2%)	**40 (18.2%)**	23 (4.9%)
Resulting in trial withdrawal	1 (0.2%)	1 (0.2%)	1 (0.4%)	**9 (4.1%)**	2 (0.4%)
Vaginal hemorrhage	14 (3.1%)	6 (1.3%)	9 (3.9%)	**27 (12.3%)**	16 (3.4%)
Metrorrhagia	2	3	2	**6**	3
Uterine hemorrhage	2	3	1	**6**	4
Postmenopausal hemorrhage	0	1	0	**4**	1
*events occurring after first dose and before last dose of study drug Source: AEMEDDRA dataset 15.1					

Transvaginal ultrasound (TVU)

This procedure was performed at screening and month 12, or early withdrawal. Scans were read locally. The 3 parameters evaluated, and criteria used to define "potential clinical importance", were:

- endometrial thickness
  - absolute value > 4mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

A total of 1588 subjects, or 86% of the safety population, were evaluated by TVU (see Table 151 below). One or more of the above criteria for potential clinical importance were met by 23% of subjects overall. Positive endometrial criteria, particularly absolute thickness >8 mm, were most common in subjects assigned to CE/MPA (17%) and CE.625/BZA (15%), compared to CE.45/BZA (12%), placebo (11%), and BZA 20 mg (8%). Increases in ovarian volume were similar between CE/BZA groups and placebo; detection of ovarian cysts was slightly more frequent with placebo.

Records of subjects with these "potential clinically important" findings were reviewed (blinded to treatment) by the medical monitor to identify those with "clinically important" findings. As shown in the table, clinically important endometrial thickness > 8 mm was determined in 19 subjects overall and was more frequent in CE.625/BZA and CE/MPA subjects. Clinically important ovarian cysts > 20 mm were present in 14 subjects overall and were fairly even between treatment groups. There were no subjects determined to have clinically important changes in ovarian volume.

Mean endometrial thickness increased in CE/MPA and both CE/BZA groups relative to baseline and relative to placebo (each with p<.05).

Table 151: Trial 3307: Subjects (n, %) with abnormal TVU findings

	CE 0.45 BZA 20 N=445	CE 0.625 BZA 20 N=474	BZA 20 N=230	CE 0.45 MPA 1.5 N=220	Placebo N=474
Subjects with scans, N	385	418	195	182	408
Subjects with Potentially Clinically Important Findings					
Total with abnormalities	77 (20)	102 (25)	40 (21)	51 (28)	88 (22)
Endometrial thickness, all	45 (12)	64 (15)	16 (8)	31 (17)	46 (11)
absolute value > 4mm	44 (12)	64 (15)	16 (8)	31 (17)	45 (11)
absolute value > 8mm	3 (<1)	8 (2)	0 (0)	4 (2)	2 (<1)
increase from baseline > 3mm	10 (3)	27 (7)	3 (2)	9 (5)	12 (3)
increase from baseline > 5mm	4 (1)	10 (2)	0 (0)	5 (3)	2 (<1)
Ovarian volume increase from baseline ≥ 2 cm^3	23 (8)	23 (7)	17 (12)	13 (9)	25 (8)
Ovarian cyst visualized	21 (7)	31 (9)	18 (12)	15 (11)	39 (12)
Subjects with Clinically Important Findings					
Endometrial Thickness >8mm	3 (0.8)	9 (2.2)	0	5 (2.8)	2 (0.5)
Ovarian Cyst >20mm	2 (0.4)	5 (1.1)	4 (1.7)	1 (0.5)	2 (0.4)

Source: CSR Tables 10-33, 10-34, 10-36

Endometrium related AEs

AEs of endometrial hypertrophy, based on increased TVU measured endometrial thickness, were reported in 1 CE.45/BZA subject, 3 CE.625/BZA subjects, 3 CE/MPA subjects and 2 placebo subjects.

Endometrial polyps identified by hysteroscopy (reported separately from endometrial polyps identified on biopsy) were reported in 4 CE.625/BZA subjects, 1 BZA 20 mg subject, 3 CE/MPA subjects and 1 placebo subject.

See section 6.4 of NDA clinical review for further details.

Other uterine related AEs

As noted above, uterine leiomyoma treatment emergent AEs were more frequent with CE/MPA than the other groups. One CE.625/BZA subject (#701556), age 53 y/o, was withdrawn from the trial at day 336, attributed to a uterine leiomyoma, also with AEs of uterine bleeding and abdominal pain; no narrative was provided but the medical history does not include pre-existing leiomyoma.

Other uterine AEs (adnexal pain, uterine cyst/ polyp/ prolapse) were nonserious, infrequent and did not show appreciable treatment group differences.

Cervix-related AEs

As **Table**152 indicates, AEs related to the cervix were similar across treatment groups. None were considered serious or resulted in trial withdrawal.

Table 152: Trial 3307: Subjects with cervix related AEs during/following therapy

Preferred term	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Any cervix related AE	10 (2.2%)	9 (1.9%)	2 (0.9%)	5 (2.3%)	9 (1.9%)
Cervicitis	0	1	0	0	0
Smear cervix abnormal	1	1	0	2	0
Cervical dysplasia	5	5	2	3	8
Cervical polyp	4	2	0	0	1
Source: CSR Table 10-12					

Vaginal AEs

Consistent with Prempro labeling, incidence of vulvovaginal candidiasis/ mycotic infection was greater with CE/MPA (3.2%) than placebo (0.6%); incidence with CE/BZA was intermediate (1.1-2.5%). There were no marked treatment group differences in incidence of vaginal discharge, atrophic vulvovaginitis or vulvovaginal dryness (see **Table**153).

Table 153: Trial 3307: Selected vaginal AE categories

	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Any vagina related AE	24 (5.4%)	38 (8.0%)	11 (4.8%)	13 (5.9%)	26 (5.5%)
Any AE of vaginal infection	14 (3.1%)	19 (4.0%)	3 (1.3%)	8 (3.6%)	9 (1.9%)
Vulvovaginal candidiasis + Vulvovaginal mycotic infection	5 (1.1%)	12 (2.5%)	1 (0.4%)	7 (3.2%)	3 (0.6%)
Vaginal discharge	6 (1.3%)	7 (1.5%)	2 (0.9%)	4 (1.8%)	10 (2.1%)
Atrophic vulvovaginitis + Vulvovaginal dryness	3 (0.6%)	6 (1.2%)	4 (1.7%)	1 (0.5%)	3 (0.6%)
Source: CSR Table 10-16					

Ovarian AEs

There were no ovarian neoplasms in the trial. AEs of ovarian cysts were reported in 18 subjects (1%), with similar incidence among treatment groups. (Many of these were identified by protocol specified TVU as discussed above.) These were all simple cysts; in addition one subject (#703628) in BZA 20 mg group had an AE of ovarian mass; this was a 12-mm left ovarian complex anechoic mass lesion discovered by TVU on day 362; no follow-up was considered to be indicated.

Table 154: Trial 3307: Ovarian cyst AEs

	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Subjects with ovarian cyst AE	3 (0.7%)	5 (1.1%)	2 (0.9%)	3 (1.4%)	5 (1.1)

Source: CSR Table 10-15

Fractures

Fractures, which were collected as regular AEs, occurred in 1.7% of subjects overall, with no appreciable difference between groups. Events surrounding the fractures were in general not provided, but verbatim terms did not suggest any low-trauma events (Table 155).

Table 155: Trial 3307: Subjects with clinical fractures during/following therapy

Site	**CE 0.45mg BZA 20 mg** N=445	**CE 0.625mg BZA 20 mg** N=474	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Any site	10 (2.2%)	4 (0.8%)	5 (2.2%)	5 (2.3%)	7 (1.5%)
Clavicle	-	-	1	-	-
Humerus	-	-	-	-	1
Elbow	-	1	-	-	1
Radius	-	1	-	-	-
Wrist	3	-	1	-	1
Hand	1	-	-	-	1
Rib	-	-	-	1	1
Thoracic vertebral	-	1	-	-	-
Sacrum	1	-	-	-	-
Pelvis	1	-	-	-	-
Ankle	2	1	1	-	-
Foot	2	-	2	3	2
Patella	-	-	-	1	1

Source: CSR Table 10-18 and AEMEDDRA

Cholelithiasis

Gallbladder disease, reportedly associated with estrogen therapy, was an exclusion criterion unless the subject was S/P cholecystectomy. During the trial, 3 subjects (709771, 700519, and 700503, treated with CE.625/BZA, CE/MPA, placebo respectively) became symptomatic for cholecystitis/cholelithiasis and underwent routine laparoscopic cholecystectomy.

Neurologic SAEs

There were also 3 subjects who experienced neurologic SAEs:

- Subject 714893, a 58 y/o woman with history of hypertension and migraines with visual symptoms, was assigned to **CE0.625/BZA**. On trial day 273 she experienced transient partial loss of vision in L eye diagnosed as **migraine with aura**. Study drug was stopped. Subsequent brain CT and carotid CTA were normal.
- Subject 702453, a 47 y/o woman with with history of hypertension and migraines, was assigned to **CE/MPA**. On day 30 and then again on day 43, she was hospitalized with complaints of **migraine** headache and fever. The symptoms resolved and she continued the study drug and completed the trial.
- Subject 700364, a 56 y/o woman with history of epilepsy maintained on topiramate, who was assigned to **placebo**. On day 298 she was hospitalized for neurologic symptoms which were diagnosed by EEG as **complex partial seizures**. She recovered, continued study drug and completed the trial.

Laboratory Adverse Events:

Abnormal liver function tests

There were 8 subjects who developed LFT elevations which, at least in part, contributed to discontinuation of treatment:

CE.45/BZA:

- Subject 701892, a 58 y/o woman had mild elevations at 4 months of ALT 80, AST 46, and GGT 87, and discontinued study drug; one month later labs were normal.
- Subject 703403, a 54 y/o woman, had elevations at 7 mos of AST 82, ALT 84 and discontinued drug; within 2 wks labs returned to normal.
- Subject 705306, a 55 y/o woman, had elevated GGT of 207 (normal 0-45) at 3 mos, resolved after discontinuation; all other LFTs remained normal.

CE.625/BZA:

- Subject 714043, a 56 y/o woman with h/o ulcerative colitis and multiple concomitant meds, presented on trial day 210 with nausea, abdominal pain, fatigue and elevated ALT 148, AST 78, AP 202 (normal 32-91). Hepatitis panel was negative; MRCP and U/S showed cholelithiasis but non inflamed GB; EGD showed gastritis, + H. pylori. Study drug was stopped and enzymes returned to normal.

- Subject 703153, a 57 y/o woman, at 3 mo visit had elevated AST 142 and ALT 215, normal AP and bilirubin; drug was stopped and levels declined slowly to normal over 3 months.
- Subject 706787, a 53 y/o woman, had elevated ALT 187 and AST 118 at 6-7 months and stopped study drug; levels declined 1 mo later; AP and bili remained normal.

CE/MPA:

- Subject 701172, a 54 y/o woman treated with gabapentin and cyclobenzaprine for fibromyalgia, had elevated LFTs at 3 mos: ALT 151 and AST 313, normal AP (106) and normal bili. Repeat labs 17 days later showed further increase with ALT 240 and AST 553, elevated AP 154. Study drug was discontinued and enzymes declined to near normal 3 weeks later.

Placebo:

- Subject 700503, a 56 y/o woman with multiple concomitant meds, was noted on 6 month labs to have elevated ALT 388, AST 374, AP 215 (normal 20-125), and GGT 275 (normal 0-45). Three weeks later she experienced biliary colic and cholelithiasis/ cholecystitis and underwent cholecystectomy.

Reviewer comment: Except for the last (placebo) subject in whom LFT elevation was probably related to cholelithiasis, these LFT elevations, occurring at 3-7 mos of treatment, were likely estrogen-related. One of the CE/BZA subjects (714043) was symptomatic. None of the events progressed to significant cholestasis, perhaps because abnormalities were detected on frequent blood draws leading to drug discontinuation.

Laboratory Mean Changes from Baseline

Consistent with anti-bone-resorptive effects of estrogens and SERMs, there were small, statistically significant decreases from baseline in serum alkaline phosphatase for all 4 active treatment groups compared to placebo, and in serum calcium and phosphorus for both CE/BZA groups compared to placebo.

CE/BZA groups showed significant declines in mean serum bilirubin and ALT relative to baseline and placebo; mean AST showed essentially no change in any group.

CE/BZA groups, relative to placebo, had small but significant decreases in mean serum creatinine, BUN, glucose, total and LDL cholesterol; and significant increases in HDL cholesterol and triglycerides.

Hemoglobin, hematocrit and platelet count all showed statistically significant mean declines in the CE/BZA groups relative to baseline and to placebo; however changes were small and probably insignificant clinically.

Four coagulation parameters were measured: 3 anti-thrombotic factors (antithrombin III, protein C, protein S) and 1 pro-thrombotic factor (PAI). Compared to placebo, CE/BZA

groups were associated with significant declines in antithrombin III, and inconsistent changes in other parameters.

Vital Signs

The number of subjects with BP increases of potential significance was slightly greater with CE/BZA or CE/MPA compared to placebo, consistent with known potential of estrogen treatment. There were slightly more placebo subjects with weight gain (≥15% and ≥25 lb.), compared to the other groups. Mean changes in BP and weight were not statistically different between groups.

Electrocardiograms

There were 6 subjects (two in each CE/BZA group, two in placebo) with various types of ECG abnormalities of "potential clinical importance" with cardiologist referral; none resulted in major therapeutic interventions.

Safety Conclusions

In trial 3307, the overall incidences of AEs (86-88%), SAEs (3.6-3.8%), and AEs resulting in trial discontinuation (7.0-7.6%) were similar among both CE/BZA dose groups and the placebo group. There were no deaths associated with CE/BZA. The CE/MPA comparison group, compared to all other groups, was notable for a higher incidence of SAEs (5.9% vs. 2.2-3.8%), and discontinuations due to an AE (14.1% vs. 7.0-7.6%).

An increased risk of thromboembolic events with CE/BZA is expected given that CE and BZA individually are associated with substantially increased risk. In trial 3307, one subject developed DVT of the lower extremity after about 3 months of CE/MPA treatment. Although there were no venous thromboembolic events in either CE/BZA group, the number of subjects was insufficient to rule out a thromboembolic risk equivalent to or perhaps even higher than CE/MPA.

One subject, a 54 y/o woman with multiple risk factors including a patent foramen ovale, experienced a CVA in the third month of treatment with CE 0.625/BZA, which is likely to have been treatment related. There were no other subjects with CVA during the trial. Two subjects, one on CE 0.45/BZA and one on placebo, and each with multiple cardiac risk factors, experienced acute MI toward the end of the treatment period. No other trial events appear to be attributable to coronary disease, with the possible exception of a placebo subject who died suddenly, perhaps related to undiagnosed cardiac disease, but with no autopsy. It is unclear from the trial whether the cardiovascular risks of CE/BZA differ from those of CE/MPA or placebo.

Reproductive disorders, particularly AEs of breast tenderness and vaginal bleeding, were more common in the CE/MPA group compared with the others as expected, and resulted in an overall excess of trial discontinuations in this arm. These AE data were consistent with data from daily diaries used to evaluate breast tenderness and bleeding/spotting as secondary endpoints, as discussed in the efficacy section of this review.

Uterine/vaginal bleeding was reported as an AE in 18% of CE/MPA subjects, compared to 2.5-5.2% of the other groups, however all events were non-serious and it appears that none led to specific intervention, other than study drug discontinuation in several cases. Bleeding was somewhat less frequent with CE/BZA (either dose) compared to placebo. One CE.625/BZA subject withdrew from the trial because of abdominal pain and bleeding, apparently related to a uterine leiomyoma, however leiomyoma incidence was no greater in the CE/BZA groups than placebo. There were no ovarian neoplasms in the trial, nor any gynecologic malignancies. Vulvovaginal candidiasis was more frequent with CE/MPA (3.2% of subjects) relative to placebo (0.6%); incidence with CE/BZA was intermediate (1.1-2.5%).

Also consistent with estrogenic effects, transvaginal ultrasound, performed in 86% of trial subjects, showed that clinically important increased thickness of endometrium was most common with CE/MPA and the higher CE/BZA dose (0.625). Mean endometrial thickness increased in CE/MPA and both CE/BZA groups relative to baseline and relative to placebo. However, treatment did not appear to have a significant effect on ovarian volume or on development of ovarian cysts.

Flushing symptoms were much less common with CE/MPA than other treatments, and were the most frequent AE associated with trial discontinuation overall. The CE/BZA groups had a lower incidence of flushing symptoms than placebo, but a slightly higher rate of discontinuation due to flushing.

There were 4 subjects with breast cancer: 2 in the CE 0.45/BZA group, 1 in the CE/MPA group and 1 on placebo. The CE/MPA subject had been previously enrolled in two CE/BZA trials, likely increasing her risk; the other 3 subjects had no previous estrogen or SERM exposure reported. Except for the placebo subject, the other 3 subjects all had family history of breast cancer. In all 4 subjects with cancer, diagnosis was initiated by the final visit mammogram at month 12. The risk of breast cancer with CE/BZA, relative to estrogen + progestin or to placebo, cannot be determined from this trial.

Seven other subjects had clinically important abnormal mammograms (BI-RADS 4 or 5) during therapy or short term follow-up, and 6 underwent biopsy showing benign disease. These events were evenly distributed among treatment groups, as were subjects with other breast related findings not warranting biopsy including other mammographic abnormalities, calcifications, cysts and masses.

Bone fractures were reported by 1.7% of trial subjects, with no appreciable difference between treatment groups. The trial was not powered to evaluate fractures.

Two subjects with history of migraines, one assigned to CE 0.625/BZA and the other to CE/MPA, were hospitalized during the treatment period due to migraines, which may be associated with estrogens.

Gastrointestinal AEs, and discontinuations related to GI AEs, were slightly more frequent in CE/BZA subjects compared with placebo. Symptomatic cholecystitis resulted in surgery for 1 subject each in the CE.625/BZA, CE/MPA and placebo groups.

Liver enzyme elevations, likely estrogen-related, occurred after 3-7 months of treatment with CE.45/BZA (n=3), CE.625/BZA (n=3) and CE/MPA (n=1), resulting in treatment discontinuations; there were no similar episodes with placebo. Mean levels of serum lipids changed as expected with estrogen treatment. There were no unexpected laboratory findings.

Study 305

Protocol 3115A1-305-US: A double-blind, randomized, placebo–controlled, efficacy and safety study of bazedoxifene/conjugated estrogens combinations for treatment of vasomotor symptoms associated with menopause.

Event Rates

Safety event rates for Trial 305 are shown in Table 156. Treatment emergent adverse events occurred in similar percentages of subjects across treatment groups (77 subjects (61%) in the BZA 20 mg/CE 0.45 mg treatment group, 86 subjects (67%) in the BZA 20 mg/CE 0.625 mg treatment group, and 46 subjects (73%) in the placebo group). No deaths occurred, and relatively few serious adverse events were reported. The percentage of subjects withdrawn for AEs was numerically but not statistically lower for active drug treatment groups than placebo. The number of subjects who withdrew for other reasons than adverse event but had an ongoing treatment emergent adverse event was low in the active treatment groups.

Table 156: Trial 305 Safety Event Rates

	BZA20/CE0.45 N=127	BZA20/CE0.625 N=128	Placebo N=63	P-value[1]
	n (%)	n (%)	n (%)	
Any TEAE	77 (61)	86 (67)	46 (73)	0.215
Deaths	0	0	0	
SAE	2 (2)	2 (2)	0	0.606
Withdrawal for AE	5 (4)	3 (2)	6 (10)	0.071
Other WD with TEAE	2 (2)	3 (2)	3 (5)	

Source: Clinical Study Report 67461, Table 10-4, Supportive Tables 15.42 and 15.44, and text pg. 66
1 P-value for Chi-square

Exposure

A total of 318 subjects were randomized and took at least one dose of study drug and are included in safety evaluations; 127 subjects in the BZA 20 mg/CE 0.45 mg treatment group, 128 subjects in the BZA 20 mg/CE 0.625 mg treatment group, and 63 subjects in the placebo group. Most subjects completed the 12 weeks of the trial; 113 subjects (89%) in the BZA 20 mg/CE 0.45 mg treatment group, 111 subjects (87%) in the BZA 20 mg/CE 0.625 mg treatment group, and 53 subjects (84%) in the placebo group. Dropout rate appeared generally linear over time.

Compliance was measured weekly. To be compliant, subjects had to take at least 80% of study drug per week (i.e. at least 6 (b) (4)). More than 85% of the subjects were compliant with test article at each time interval, with no difference among groups. If Week 12 is excluded (the last week of study dosing), at least 94% of subjects were compliant for all treatment groups at each time interval.

Deaths

No deaths were reported during the study.

Serious Adverse Events

A total of four serious adverse events were reported:
BZA 20 mg/CE 0.45 mg:

- A 56 year old woman had a forehead skin lesion excised during the screening period. The subject reported the lesion was benign. She was randomized and completed the study. The pathology report, obtained after completion of the study, indicated basal cell carcinoma which extended to the margins of the biopsy. Mohs excisional surgery was performed.
- A 54 year old woman was hospitalized with epigastric pain, nausea, and vomiting on Study Day 68. Ultrasound demonstrated cholelithiasis with an impacted stone in the gallbladder neck. She underwent laparoscopic cholecystectomy without complications and completed the study.

BZA 20 mg/CE 0.625 mg:

- A 55 year old woman was involved in a MVA on Study Day 47 with fractures of the right foot requiring surgical reduction. She completed the study.
- A 45 year old woman took 30 extra doses of study medicine from Day 1 to Day 49. She reported taking a dose in the afternoon as she could not recall taking her morning dose. No AEs were reportedly associated with the overdose, although the subject had elevated blood pressure (162/55) at Week 4 which returned to normal without treatment at Week 8 and had mild hair loss from Study Days 14 through 73. The overdose was not discovered until the end of the study. The subject was discontinued for protocol violation. This event was reported as an SAE as the amount of additional study medication taken was considered clinically important (i.e. medially important).

Placebo:

- None

Estrogens have been associated with cholelithiasis. No concerning patterns of serious adverse events are noted other than that association. Although not a serious adverse event, alopecia has also been associated with estrogen use.

Adverse Events Leading to Withdrawal

A total of 14 subjects withdrew from the study for adverse events; 5 (4%) in the BZA 20 mg/CE 0.45 mg treatment group, 3 (2%) in the BZA 20 mg/CE 0.625 mg treatment group, and 6 (10%) in the placebo group. Cases included:

BZA 20 mg/CE 0.45 mg:

- A 55 year old woman discontinued study medicine on Study Day 21 and withdrew on Day 43 with chest pain and flatulence. The chest pain was thought by the investigator to be non-cardiac. The subject experienced nephrolithiasis after discontinuing study medicine, but the chest pain and flatulence continued after the nephrolithiasis resolved.
- A 54 year old woman withdrew on Study Day 63 with chest pain. The clinic physician thought the chest pain was musculoskeletal in nature but recommended an ECG which the subject refused.
- A 57 year old woman with a history of irritable bowel discontinued study medicine on Study Day 23 and withdrew on Day 49 for abdominal pain.
- A 51 year old woman discontinued study medicine on Study Day 60 and withdrew on Day 97 for intermittent abdominal pain.
- A 54 year old woman discontinued study medicine on Study Day 1 and withdrew on Day 3 for nausea.

BZA 20 mg/CE 0.625 mg:

- A 52 year old woman discontinued study medicine on Study Day 33 and withdrew on Day 124 with hypertension. Blood pressure at Baseline was 148/88 and at Week 4 was 174/111. The subject was started on losartan and referred to her primary care doctor.
- A 48 year old woman discontinued study medicine on Study Day 26 and withdrew on Day 41 for back pain, leg cramps, and hypoalgesia.

- A 51 year old woman discontinued study medicine on Study Day 14 and withdrew on Day 56 for depression.

Placebo:

- A 61 year old woman discontinued study medicine on Study Day 41 and withdrew on Day 77 because of an episode of dizziness with negative ECG, CT brain, carotid ultrasound, and neurologic consultation.
- A 61 year old woman discontinued study medicine on Study Day 28 and withdrew on Day 45 for worsening of hot flashes.
- A 57 year old woman with a history of GERD discontinued study medicine on Study Day 34 and withdrew on Day 146 for recurrent GERD.
- A 51 year old woman with a history of depression discontinued study medicine on Study Day 35 and withdrew on Day 50 for depression.
- A 53 year old woman discontinued study medicine on Study Day 55 and withdrew on Day 90 for emotional lability.
- A 63 year old woman discontinued study medicine on Study Day 56 and withdrew on Day 71 for urticaria.

No concerning patterns are noted in withdrawals for adverse events.

Adverse Events Leading to Dose Alteration

No other adverse events were found to have led to study drug discontinuation or dose reduction.

Adverse Events On- and Post-treatment

On- and post-treatment adverse events for Trial 305 which occurred in at least 5% of subjects in a treatment group are shown in 17. Totals differ from Table 157 as AEs in the 15 day post-treatment period are included.

In general, adverse events were similar within treatment groups. More sinusitis was reported in the placebo group (4 subjects (3%) in the BZA 20 mg/CE 0.45 mg treatment group, 1 subject (1%) in the BZA 20 mg/CE 0.625 mg treatment group, and 5 subjects (8%) in the placebo group). A few other adverse events showed significant differences between groups without any treatment group reaching 5% of subjects reporting the event; flatulence in 4 subjects (3%) in the BZA 20 mg/CE 0.45 mg treatment group with no other subjects reporting this AE, procedural pain in one subject (1%) in the BZA 20 mg/CE 0.45 mg treatment group and 3 subjects (4.8%) on placebo, and rash in 4 subjects (3%) in the BZA 20 mg/CE 0.625 mg treatment group with no other subjects reporting this AE. The lack of concordance between the bazedoxifene/conjugated estrogen treatment groups for flatulence and rash increases uncertainty in attributing those adverse events to the treatment.

A review of treatment emergent AEs only (no 15 day post-treatment adverse events) produced generally similar results except fewer treatment groups reached 5% of subjects reporting particular AEs.

Table 157: Trial 305 On- and Post-treatment Adverse Events Reported by at least 5% of Subjects in a Treatment Group

SOC Preferred term[2]	BZA20/CE0.45 N=127	BZA20/CE0.625 N=128	Placebo N=63	P-value[1]
	n (%)	n (%)	n (%)	
Any AE[3]	88 (69)	98 (77)	47 (75)	0.408
Nervous system	39 (31)	37 (29)	18 (29)	0.934
Headache	32 (25)	29 (23)	16 (25)	0.868
Infections and infestations	31 (24)	29 (23)	18 (29)	0.670
Nasopharyngitis	14 (11)	10 (8)	3 (5)	0.324
Upper resp. tract infection	3 (2)	5 (4)	5 (8)	0.187
Sinusitis	4 (3)	1 (1)	5 (8)	0.029*
Gastrointestinal	33 (26)	28 (22)	14 (22)	0.712
Nausea	6 (5)	8 (6)	3 (5)	0.841
Diarrhea	8 (6)	4 (3)	2 (3)	0.405
Abdominal distension	5 (4)	2 (2)	4 (6)	0.219
Musculoskeletal and C.T.	29 (23)	25 (20)	21 (33)	0.104
Back pain	11 (9)	10 (8)	5 (8)	0.967
Arthralgia	10 (8)	9 (7)	5 (8)	0.960
Muscle spasms	4 (3)	8 (6)	3 (5)	0.506
Pain in extremity	6 (5)	4 (3)	5 (8)	0.337
Myalgia	5 (4)	2 (2)	4 (6)	0.219
Reproductive and breast	15 (12)	17 (13)	5 (8)	0.554
Psychiatric	9 (7)	14 (11)	10 (16)	0.168
Insomnia	5 (4)	8 (6)	4 (6)	0.660
Respiratory, thoracic, & med.	15 (12)	12 (9)	2 (3)	0.149
General and admin. site	10 (8)	9 (7)	7 (11)	0.618
Injury, poison., & proc. comp.	8 (6)	12 (9)	4 (6)	0.599
Skin and subcutaneous tissue	7 (6)	9 (7)	3 (5)	0.791
Vascular	9 (7)	7 (5)	3 (5)	0.778
Investigations	6 (5)	5 (4)	5 (8)	0.478

Source: NDA022247, GSR 0007, 5.3.5.1.3 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Adverse Events of Special Interest:

Venous Thromboembolism (VTE)

Venous thromboembolism has been a concern both with estrogens and bazedoxifene monotherapy. No venous thromboembolism events were reported in this trial.

Other Vascular Events

Cerebrovascular events have been a concern both with estrogens and bazedoxifene monotherapy. No cerebrovascular events were reported in the trial.

The AE of chest pain was reported by 4 subjects (3%) in the BZA 20 mg/CE 0.45 mg treatment group and 2 subjects (3%) in the placebo group. A cardiac origin was not suspected in any of these subjects. No myocardial infarction or angina was reported.

A single non-serious case of tachycardia was reported in the BZA 20 mg/CE 0.45 mg treatment group and a single non-serious case of palpitations was reported in the BZA 20 mg/CE 0.625 mg treatment group.

Malignancy

No malignancies, including endometrial or breast cancer, were reported in this trial. As the trial was 12 weeks in duration with a 2 week follow-up, lack of malignancy is not surprising.

Breast Disorders Reported as Adverse Events

Adverse events of breast swelling were reported by two subjects in the BZA 20 mg/CE 0.45 mg treatment group, one of whom also had breast tenderness. Another subject in the same treatment group reported breast tenderness. Breast pain was reported by two subjects in the BZA 20 mg/CE 0.45 mg treatment group and one subject in the BZA 20 mg/CE 0.625 mg treatment group. No subject in the placebo group reported an adverse event of breast swelling, tenderness, or pain. These AEs did not lead to withdrawal or dose change for any subject. Note breast pain was also an efficacy measure.

Uterine Disorders Reported as Adverse Events

All uterine and vaginal adverse events in Trial 305 are shown inTable 158. Transvaginal ultrasound was performed at Baseline and Week 12 and is discussed in Dr Gerald Willett's review of uterine safety. Endometrial biopsy was performed for subjects with endometrial thickness greater than 4 mm at Week 12 and is also discussed in Dr. Willett's review.

Overall, little difference is noted for any preferred term uterine or vaginal adverse event or for bleeding, although numbers are small. No cases of bleeding were reported to require medical attention or result in a reduction in hematocrit.

Table 158: Trial 305 Uterine and Vaginal Disorders Reported as Adverse Events on and after Therapy

	BZA20/CE0.45 N=127	BZA20/CE0.625 N=128	Placebo N=63
	n (%)	n (%)	n (%)
Any uterine or vaginal event	12 (9)	16 (13)	6 (10)
Any bleeding event	6 (5)	4 (3)	3 (5)
Coital bleeding	1 (1)	0	0
Uterine hemorrhage	1 (1)	0	1 (2)
Vaginal hemorrhage	3 (2)	4 (3)	3 (5)
Withdrawal bleeding	1 (1)	0	0
Other uterine or vaginal event			
Adenexa uteri pain	0	2 (2)	0
Dysmenorrhea	2 (2)	1 (1)	0

	BZA20/CE0.45 N=127	BZA20/CE0.625 N=128	Placebo N=63
Endometrial hypertrophy	1 (1)	3 (2)	0
Pelvic pain	1 (1)	0	1 (2)
Uterine cyst	0	1 (1)	0
Vaginal discharge	1 (1)	3 (2)	1 (2)
Vulvovaginal discomfort	0	1 (1)	0
Vulvovaginal dryness	2 (2)	0	0
Vulvovaginal pain	0	1 (1)	0
Vulvovaginal pruritis	0	1 (1)	0
Source: NDA022247, GSR 0007, 5.3.5.1.25.2.1 (Information request response)			

Laboratory:

Laboratory Adverse Events

Few laboratory findings were reported as adverse events in Trial 305 as noted inTable 159. Estrogen therapy has been associated with increased triglyceride levels, but that is not noted in this study (see also **Table**). Bazedoxifene monotherapy has been associated with increased transaminases, but that is not noted in this study (see also **Table**).

Table 159: Trial 305 Laboratory Events Reported as Adverse Events

SOC Preferred term[2,3]	BZA20/CE0.45 N=127	BZA20/CE0.625 N=128	Placebo N=63	P-value[1]
	n (%)	n (%)	n (%)	
Investigations				
ALT increased	0	0	1 (2)	0.131
AST increased	0	0	1 (2)	0.131
Cholesterol increased	1 (1)	3 (2)	0	0.326
Potassium increased	0	0	1 (2)	0.131
Sodium increased	0	1 (1)	0	0.475
Triglycerides increased	0	0	1 (2)	0.131
LDL increased	0	2 (2)	0	0.225
Metabolism & nutr. disorders				
Hypercholesterolemia	1 (1)	0	0	0.470

Source: NDA022247, GSR 0007, 5.3.5.1.3 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Marked Laboratory Abnormalities

Table 160 shows numbers of subjects with laboratory abnormalities predetermined to be of potential clinical significance where at least two subjects in a treatment group for a particular test were in the significant range. In no case did subjects in the test drug groups appear to have potentially significant lab results more commonly that subjects in the placebo group.

Table 160: Trial 305 Subjects with On-therapy Lab Results of Potential Clinical Importance, (at least 2 Subjects in a Treatment group)

Test	Range	BZA20/CE0.45 N=125[2]	BZA20/CE0.625 N=126[2]	Placebo N=61[2]	P-value[1]
		n (%)	n (%)	n (%)	
Total		9 (7)	12 (10)	11 (18)	0.069
Glucose, fasting	>125 mg/dL	2 (2)	1 (1)	0	0.557
Uric acid	>7.3 mg/dL	1 (1)	3 (2)	2 (3)	0.456
AST	≥3X ULN	0	0	2 (3)	0.016
ALT	≥3X ULN	0	0	2 (3)	0.016
AST[3]	≥1.5X ULN	2 (2)	4 (3)	4(7)	
ALT[3]	≥1.5X ULN	1 (1)	2 (2)	5 (8)	
Alk. Phos.	≥1.5X ULN	2 (2)	0	2 (3)	0.161
Triglycerides, fasting[3]	>330 mg/dL	1 (1)	2 (2)	4(7)	0.040

Source: Clinical Study Report 67461, Tables 10.8, 10-9, and datasets
1 P-value for Chi-square
2 Some denominators for particular labs were slightly lower
3 The Statistical Analysis Plan called for AST and ALT to be analyzed at both 1.5X and 3X ULN. The Applicant reports 3X was determined to be the more relevant value and 1.5X was not analyzed, (but was taken from datasets). Similarly, for triglycerides, the additional criterion of an increase from Baseline of at least 50 mg/dL (with the level > 330 mg/dL) was dropped

A 63 year old woman randomized to the BZA 20 mg/CE 0.625 mg treatment group entered the study with as hematocrit of 33.7% and hemoglobin of 10.0 g/dL. At 4 and 12 weeks these had fallen to 28.9% and 8.9 g/dL and then 28.2% and 8.7 g/dL. The subject was reportedly asymptomatic, did not experience bleeding, and completed the study. The investigator did not report the decrease in hematocrit or hemoglobin as an adverse event and no additional testing was performed.

Mean Change from Baseline

Estrogen therapy has been associated with elevation of HDL cholesterol and triglycerides. Bazedoxifene/conjugated estrogen was associated with mild mean decreases in total and LDL cholesterol from Baseline to Week 12 (total, -17 mg/dL for BZA 20 mg/CE 0.45 mg, -15 mg/dL for BZA 20 mg/CE 0.625 mg; LDL, -19 mg/dL for BZA 20 mg/CE 0.45 mg, -17 mg/dL for BZA 20 mg/CE 0.625 mg) and slight increases in triglycerides (10 mg/dL for BZA 20 mg/CE 0.45 mg, 13 mg/dL for BZA 20 mg/CE 0.625 mg). HDL cholesterol was essentially unchanged. These changes are not likely to be clinically significant.

Bazedoxifene monotherapy has been associated with elevated transaminases. Bazedoxifene/conjugated estrogen was associated with slight mean decreases from Baseline to Week 12 in ALT (-2 U for BZA 20 mg/CE 0.45 mg, -3 U for BZA 20 mg/CE 0.625 mg) but little change for AST. Alkaline phosphatase showed mild reduction (-7 U for BZA 20 mg/CE 0.45 mg, -8 U for BZA 20 mg/CE 0.625 mg, perhaps antiresorptive effect). Total bilirubin showed a statistically but probably not clinically significant reduction of -0.1 mg/dL in both active treatment groups.

Bazedoxifene/conjugated estrogen was associated with slight mean decreases from Baseline to Week 12 in calcium (-0.3 mg/dL for both active treatment groups) and phosphorus (-0.4 mg/dL for BZA 20 mg/CE 0.45 mg, -0.3 mg/dL for BZA 20 mg/CE 0.625 mg).

No mean change from Baseline to Week 12 was noted for creatinine. No clinically significant change was noted for BUN.

Bazedoxifene/conjugated estrogen was associated with slight mean decreases in hemoglobin and hematocrit from Baseline to Week 12 (hemoglobin, -0.3 g/dL for BZA 20 mg/CE 0.45 mg, -0.4 g/dL for BZA 20 mg/CE 0.625 mg; hematocrit, -0.8% for BZA 20 mg/CE 0.45 mg, -0.9% for BZA 20 mg/CE 0.625 mg). These changes are not clinically significant.

Shifts

Shift tables for laboratory were not provided.

Vital Signs

A total of 9 subjects were reported as having AEs of hypertension during the study: 3 subjects (2%) in the BZA 20 mg/CE 0.45 mg treatment group, 4 subjects (3%) in the BZA 20 mg/CE 0.625 mg treatment group, and 2 subjects (3%) in the placebo group. Estrogens have been reported to increase blood pressure in some patients, but that is not apparent for hypertension as an adverse event.

A potentially clinically important increase from baseline of systolic BP was defined as ≥ 20 mm Hg increase with absolute value of ≥ 160 mm Hg. This occurred on-therapy for 1 of 125 subjects (1%) in the BZA 20 mg/CE 0.45 mg treatment group, 4 of 127 subjects (3%) in the BZA 20 mg/CE 0.625 mg treatment group, and none of 61 subjects in the placebo group. A clinically important increase from baseline of diastolic BP was defined as ≥ 15 mm Hg increase with absolute value ≥ 90 mm Hg. This occurred on-therapy for 6 subjects (5%) in the BZA 20 mg/CE 0.45 mg treatment group, 6 subjects (5%) in the BZA 20 mg/CE 0.625 mg treatment group, and 3 subjects (5%) in the placebo group. Not all subjects with potentially clinically important increases of blood pressure were reported as adverse events.

A potentially clinically important decrease from baseline of systolic BP was defined as ≥ 20 mm Hg decrease with absolute value of ≤ 90 mm Hg and occurred in a single subject in the BZA 20 mg/CE 0.625 mg treatment group. A potentially clinically important decrease from baseline of diastolic BP was defined as ≥ 15 mm Hg decrease with absolute value of ≤ 60 mm Hg. This occurred on-therapy for 3 subjects (2%) in the BZA 20 mg/CE 0.45 mg treatment group, 4 subjects (3%) in the BZA 20 mg/CE 0.625 mg treatment group, and 2 subjects (3%) in the placebo group.

Mean change in systolic and diastolic blood pressure over the 12 weeks of the study was small and not different from placebo. Systolic blood pressure increased by a mean of 1.3 mmHg in the BZA 20 mg/CE 0.45 mg treatment group, 2.3 mmHg in the BZA 20 mg/CE 0.625 mg treatment group, and 1.0 mmHg in the placebo group. Diastolic blood pressure increased by a mean of 1.1 mmHg in the BZA 20 mg/CE 0.45 mg treatment group, 1.1 mmHg in the BZA 20 mg/CE 0.625 mg treatment group, and 1.4 mmHg in the placebo group.

Significant blood pressure increase was not seen with the bazedoxifene/conjugated estrogen in this study.

Weight increased was reported as an adverse event in 4 subjects (3%) in the BZA 20 mg/CE 0.45 mg treatment group, no subjects in the BZA 20 mg/CE 0.625 mg treatment group, and 2 subjects (3%) in the placebo group. A single subject on placebo had a potentially clinically important weight gain of ≥ 15% and ≥ 25 pounds over the course of the study. This was not reported as an adverse event. Weight increased by a mean of 0.0 kg in the BZA 20 mg/CE 0.45 mg treatment group, 0.7 kg in the BZA 20 mg/CE 0.625 mg treatment group, and 1.0 kg in the placebo group. The BZA 20 mg/CE 0.45 mg treatment group weight increase was statistically less than placebo.

Safety Conclusions

In this 12 week trial of 318 subjects (safety population) with two arms of active drug against placebo at a 2:2:1 ratio, both doses of bazedoxifene/conjugated estrogen were well-tolerated. Treatment emergent adverse events occurred in similar percentages of subjects across treatment groups (77 subjects (61%) in the BZA 20 mg/CE 0.45 mg treatment group, 86 subjects (67%) in the BZA 20 mg/CE 0.625 mg treatment group, and 46 subjects (73%) in the placebo group). No deaths or malignancies were reported. No patterns of withdrawal for adverse events were associated with active therapy. No serious adverse events or common adverse events appeared associated with active therapy with the possible exception of an SAE of cholelithiasis in the BZA 20 mg/CE 0.45 mg treatment group.

With estrogens, stroke and venous thromboembolic disorders are a concern. None were reported in this trial. A few adverse events of breast swelling, tenderness, or pain did appear associated with active therapy (note breast pain was also an efficacy measure).

Refer to the section 6.4 of the clinical review (NDA 22247) for further review of endometrial safety.

With bazedoxifene monotherapy elevated transaminases have been found, but that was not apparent in this trial.

Study 306

Protocol 3115A1-306-WW: A double blind, randomized, placebo and active controlled efficacy and safety study of bazedoxifene/conjugated estrogen combinations for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women.

Event Rates

Safety event rates for Trial 306 are shown in Table 161. Treatment emergent adverse events occurred in similar percentages of subjects across treatment groups (164 subjects (75%) in the BZA 20 mg/CE 0.45 mg treatment group, 175 subjects (80%) in the BZA 20 mg/CE 0.625 mg treatment group, 90 subjects (82%) in the BZA 20 mg treatment group, and 75 subjects (71%) in the placebo group). No deaths occurred, and relatively few serious adverse events were reported. The percentage of subjects withdrawn for AEs was numerically lower for the combination drug treatment groups than bazedoxifene monotherapy and placebo. The number of subjects who withdrew for other reasons than adverse event but had an ongoing treatment emergent adverse event was low.

Table 161: Trial 306 Safety Event Rates

	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Any TEAE	164 (75)	175 (80)	90 (82)	75 (71)	0.160
Deaths	0	0	0	0	
SAE	1 (<1)	2 (1)	1 (1)	3 (3)	
Withdrawal for AE	7 (3)	9 (4)	8 (7)	7 (7)	0.290
Other WD with TEAE	3 (1)	3 (1)	1 (1)	0	

Source: Clinical Study Report 67466, Table 10-4, Supportive Tables 15.75 and 15.77, and text pg. 68
1 P-value for Chi-square

Exposure

A total of 652 subjects were randomized and took at least one dose of study drug and are included in safety evaluations; 219 subjects in the BZA 20 mg/CE 0.45 mg treatment group, 218 subjects in the BZA 20 mg/CE 0.625 mg treatment group, 110 subjects in the BZA 20 mg treatment group, and 105 subjects in the placebo group. Most subjects completed the 12 weeks of the trial; 205 subjects (94%) in the BZA 20 mg/CE 0.45 mg treatment group, 200 subjects (92%) in the BZA 20 mg/CE 0.625 mg treatment group, 99 subjects (90%) in the BZA 20 mg treatment group, and 97 subjects (92%) in the placebo group. Dropout rate appeared generally linear over time.

To be considered compliant with study treatment, subjects had to take at least 80% of study drug over the 12 weeks of the study. In each treatment group, over 98% of subjects were compliant. Only 5 subjects took less than 80% of the protocol-specified doses; 3 subjects in the BZA 20 mg/CE 0.45 mg group, no subjects in the BZA 20 mg/CE 0.625 mg group, 1 subject in the BZA 20 mg group, and 1 placebo subject.

Deaths

No deaths were reported during the study.

Serious Adverse Events

A total of seven serious adverse events were reported:
BZA 20 mg/CE 0.45 mg:

- A 59 year old woman with a benign screening mammogram had an abnormal annual screening mammogram on Day 53. Biopsy demonstrated breast cancer, and the subject was withdrawn on Day 69.

BZA 20 mg/CE 0.625 mg:

- A 64 year old woman with a history of GERD, hypertension, and hypercholesterolemia was hospitalized on Day 78 with chest pain and dyspnea relieved by nitroglycerin. Cardiac workup including a thallium stress test was negative. A cardiologist considered the chest pain atypical. The subject completed the study.
- A 48 year old woman with a history of GERD and hypertension was hospitalized on Day 73 for chest pain. Myocardial infarction was ruled out and the pain reportedly resolved with aspirin, nitro paste, sublingual nitroglycerin, and metaprolol. A second episode of mild chest pain began on Day 76, lasted 22 days, and resolved with nitroglycerin. The subject reported the AE of angina 14 days post therapy. A thallium stress test and gallbladder ultrasound were recommended but results are not available. The subject completed the study.

BZA 20 mg

- A 53 year old woman with a prior history of skin cancer developed squamous cell skin carcinoma on Day 61 which was treated. The subject completed the study.

Placebo:

- A 53 year old woman reported a drug withdrawal syndrome with venlafaxine taper with psychotic episode and hospitalization on Day 97 (after study drug treatment but in the follow-up period). The subject completed the study.
- A 56 year old woman with osteoarthritis underwent right total knee arthroplasty on Day 27. The subject completed the study.
- A 60 year old woman with osteoarthritis underwent left total hip arthroplasty on Day 92. The subject completed the study.

No concerning patterns of serious adverse events are noted. Women's Health Initiative Studies showed increased risk of breast cancer with estrogen plus progesterone but not with estrogen alone. Day 53 is early for hypothesizing a causative effect for the case considered, but estrogen is a known breast cancer promoter. However, only a single case of breast cancer is reported (in the BZA 20 mg/CE 0.45 mg treatment group).

Only one plausible case of cardiac ischemia is reported (in the BZA 20 mg/CE 0.625 mg treatment group). Women's Health Initiative Studies showed increased risk of non-fatal myocardial infarction with estrogen plus progesterone but not with estrogen alone.

Adverse Events Leading to Withdrawal

A total of 31 subjects withdrew from Study 306 for adverse events (primary or secondary cause for withdrawal but not subjects who withdrew for other reasons with an ongoing AE); 7 (3%) in the BZA 20 mg/CE 0.45 mg treatment group, 9 (4%) in the BZA 20 mg/CE 0.625 mg treatment group, 8 (7%) in the BZA 20 mg treatment group, and 7 (7%) in the placebo group. Withdrawals for adverse events are shown in Table 162. No concerning patterns are noted in withdrawals for adverse events.

Table 162: Trial 306 Adverse Events leading to Withdrawal

SOC Preferred term[2]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Withdrawal for AE	7 (3)	9 (4)	8 (7)	7 (7)	0.290
Eye	0	0	1 (1)	0	0.177
Vision blurred	0	0	1 (1)	0	0.177
Gastrointestinal	0	0	3 (3)	3 (3)	0.006*
Abdominal distention	0	0	1 (1)	0	0.177
Dyspepsia	0	0	1 (1)	0	0.177
Flatulence	0	0	0	1 (1)	0.157
Nausea	0	0	0	2 (2)	0.015*
Vomiting	0	0	1 (1)	0	0.177
General and admin. site	0	2 (1)	1 (1)	0	0.395
Chest pain	0	1 (<1)	0	0	0.574
Irritability	0	0	1 (1)	0	0.177
Malaise	0	0	1 (1)	0	0.177
Hepatobiliary	0	0	1 (1)	0	0.177
Cholecystitis, chronic	0	0	1 (1)	0	0.177
Investigations	1 (<1)	1 (<1)	1 (1)	0	0.809
Bilirubin increased	0	0	1 (1)	0	0.177
Potassium increased	1 (<1)	0	0	0	0.577
BP increased	0	1 (<1)	0	0	0.574
Musculoskeletal & C.T.	1 (<1)	1 (<1)	0	3 (3)	0.059
Arthralgia	0	0	0	1 (1)	0.157
Back pain	1 (<1)	1 (<1)	0	1 (1)	0.786
Muscle spasms	0	0	0	1 (1)	0.157
Neck pain	1 (<1)	0	0	0	0.577
Pain in extremity	0	0	0	1 (1)	0.157
Neoplasms	1 (<1)	0	0	0	0.577
Breast cancer, stage I	1 (<1)	0	0	0	0.577
Nervous system	1 (<1)	1 (<1)	0	2 (2)	0.293
Migraine	1 (<1)	1 (<1)	0	2 (2)	0.293
Psychiatric	2 (1)	1 (<1)	0	0	0.577
Anxiety	0	1 (<1)	0	0	0.574
Emotional disorder	2 (1)	0	0	0	0.265
Reproductive & breast	0	1 (<1)	0	0	0.574
Vaginal discharge	0	1 (<1)	0	0	0.574
Skin & subcutaneous	1 (<1)	0	1 (1)	0	0.483
Rash	1 (<1)	0	1 (1)	0	0.483
Vascular	1 (<1)	2 (1)	1 (1)	0	0.747

SOC Preferred term[2]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
Hypertension	1 (<1)	1 (<1)	1 (1)	0	0.809
Vein pain	0	1 (<1)	0	0	0.574

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1

Adverse Events Leading to Dose Alteration

No other adverse events were found to have led to study drug discontinuation or dose reduction.

Adverse Events ≥5 %

On- and post-treatment adverse events for Trial 306 which occurred in at least 5% of subjects in a treatment group are shown inTable 163. Totals differ from Table 161 as AEs in the 15 day post-treatment period are included. Most common adverse events were headache, back pain, hot flush, and arthralgia.

In general, adverse events were similar between treatment groups. The System Organ Class of Reproductive System and Breast Disorders showed imbalance with adverse events in this class reported by 29 subjects (13%) in the BZA 20 mg/CE 0.45 mg treatment group, 52 subjects (24%) in the BZA 20 mg/CE 0.625 mg treatment group, 21 subjects (19%) in the BZA 20 mg treatment group, and 15 subjects (14%) in the placebo group. The excess in adverse events for the BZA 20 mg/CE 0.625 mg treatment group resulted primarily from vulvovaginal pruritis (4 subjects (2%) in the BZA 20 mg/CE 0.45 mg treatment group, 12 subjects (6%) in the BZA 20 mg/CE 0.625 mg treatment group, 4 subjects (4%) in the BZA 20 mg treatment group, and 1 subject (1%) in the placebo group) and vaginal discharge (3 subjects (1%) in the BZA 20 mg/CE 0.45 mg treatment group, 10 subjects (4.6%) in the BZA 20 mg/CE 0.625 mg treatment group, no subjects in the BZA 20 mg treatment group, and 3 subjects (3%) in the placebo group), with perhaps some contribution from vulvovaginal burning (0, 5, 1, and 0 subjects respectively). It is unclear why the increase in conjugated estrogen from 0.45 to 0.625 mg may have made such a difference in vulvovaginal pruritis and burning and vaginal discharge, but this finding will be further evaluated in other studies.

The System Organ Class of Injury, Poisoning, and Procedural Complications also showed imbalance with adverse events in this class reported by 12 subjects (5%) in the BZA 20 mg/CE 0.45 mg treatment group, 15 subjects (7%) in the BZA 20 mg/CE 0.625 mg treatment group, 17 subjects (15%) in the BZA 20 mg treatment group, and 4 subjects (4%) in the placebo group. It would appear the increase in arthropod bites, contusions, joint injuries, and ligament sprains, that made up much of increase in the bazedoxifene monotherapy group was likely a matter of chance.

More migraine was reported in the placebo group (8 subjects (4%) in the BZA 20 mg/CE 0.45 mg treatment group, 4 subjects (2%) in the BZA 20 mg/CE 0.625 mg treatment group, 2 subjects (2%) in the BZA 20 mg treatment group, and 8 subjects (8%) in the placebo group). More abdominal distension was reported in the bazedoxifene monotherapy group (9 subjects (4%) in the BZA 20 mg/CE 0.45 mg treatment group, 5 subjects (2%) in the BZA 20 mg/CE 0.625 mg treatment group, 11 subjects (10%) in the BZA 20 mg treatment group, and 4 subjects (4%) in the placebo group). Why the other groups with combination bazedoxifene products did not show an increase in abdominal distension is unclear.

A few other adverse events showed differences between groups without any treatment group reaching 5% of subjects reporting the event, including seasonal allergy primarily in the bazedoxifene group (4 subjects, 4%), viral infection in placebo (2 subjects, 2%), breast enlargement in the bazedoxifene group (2 subjects, 2%), blister in the bazedoxifene group (2 subjects, 2%), and vasodilatation in the bazedoxifene group (2 subjects, 2%). These adverse events are present in small numbers and many are unlikely clinically significant based on combination product groups showing no or few subjects with that event.

Other adverse events showing differences included thirst primarily in placebo (2 subjects, 2%), weight increase primarily in BZA 20 mg/CE 0.625 mg (5 subjects, 2%), osteoarthritis primarily in placebo (2 subjects, 2%), and oropharyngeal pain primarily in BZA 20 mg/CE 0.625 mg (19 subjects, 9%). It is difficult to understand why weight increase and oropharyngeal pain should be primarily in the BZA 20 mg/CE 0.625 treatment group.

A review of treatment emergent AEs only (no 15 day post-treatment adverse events) produced generally similar results except fewer treatment groups reached 5% of subjects reporting particular AEs. Hot flush adverse events increased noticeably in the bazedoxifene/conjugated estrogen groups in the 15 days following dosing (by 6 subjects (to 21 total, 10%) in the BZA 20 mg/CE 0.45 mg group and 15 subjects (to 24 total, 11%) in the BZA 20 mg/CE 0.625 group).

Table 163: Trial 306 On- and Post-treatment Adverse Events Reported by at least 5% of Subjects in a Treatment Group

SOC Preferred term[2]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Any AE[3]	177 (81)	188 (86)	90 (82)	79 (75)	0.108
Nervous system	81 (37)	83 (38)	32 (29)	34 (32)	0.354
Headache	60 (27)	68 (31)	28 (25)	25 (24)	0.493
Migraine	8 (4)	4 (2)	2 (2)	8 (8)	0.041*
Musculoskeletal and C.T.	68 (31)	75 (34)	37 (34)	32 (30)	0.842
Back pain	23 (11)	30 (14)	17 (15)	9 (9)	0.323
Arthralgia	15 (7)	20 (9)	12 (11)	6 (6)	0.431

SOC Preferred term[2]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Pain in extremity	16 (7)	14 (6)	5 (5)	9 (9)	0.671
Myalgia	15 (7)	13 (6)	5 (5)	5 (5)	0.808
Muscle spasm	11 (5)	15 (7)	3 (3)	5 (5)	0.447
Gastrointestinal	69 (32)	63 (29)	35 (32)	29 (28)	0.845
Nausea	16 (7)	13 (6)	6 (5)	5 (5)	0.810
Diarrhea	14 (6)	8 (4)	5 (5)	7 (7)	0.529
Abdominal distension	9 (4)	5 (2)	11 (10)	4 (4)	0.015*
Constipation	4 (2)	13 (6)	7 (6)	3 (3)	0.086
Infections and infestations	53 (24)	62 (28)	30 (27)	23 (22)	0.563
Nasopharyngitis	14 (6)	19 (9)	8 (7)	8 (8)	0.835
Reproductive and breast	29 (13)	52 (24)	21 (19)	15 (14)	0.023*
Vulvovaginal pruritis	4 (2)	12 (6)	4 (4)	1 (1)	0.078
Respiratory, thoracic, & med.	29 (13)	37 (17)	13 (12)	9 (9)	0.194
Oropharyngeal pain	7 (3)	19 (9)	7 (6)	5 (5)	0.096
Vascular	26 (12)	30 (14)	20 (18)	8 (8)	0.128
Hot flush	21 (10)	24 (11)	16 (15)	7 (7)	0.280
General and admin. site	25 (11)	32 (15)	16 (15)	9 (9)	0.382
Skin and subcutaneous tissue	28 (13)	27 (12)	14 (13)	11 (10)	0.942
Psychiatric	21 (10)	34 (16)	15 (14)	9 (9)	0.153
Insomnia	14 (6)	15 (7)	12 (11)	6 (6)	0.414
Injury, poison., & proc. comp.	12 (5)	15 (7)	17 (15)	4 (4)	0.003*
Investigations	13 (6)	14 (6)	8 (7)	4 (4)	0.733
Eye	8 (4)	5 (2)	6 (5)	3 (3)	0.498

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Adverse Events of Special Interest:

Venous Thromboembolism (VTE)

Venous thromboembolism has been a concern both with estrogens and bazedoxifene monotherapy. No venous thromboembolism events were reported in this trial.

Other Vascular Events

Cerebrovascular events have been a concern both with estrogens and bazedoxifene monotherapy. No cerebrovascular events were reported in the trial except for a single case of syncope on Day 62 in a 58 year old woman in the BZA 20 mg treatment group. The only evaluation reported was an ECG which showed sinus bradycardia and possible left atrial enlargement. The subject completed the study.

Cardiac disorders and related adverse events reported in Trial 306 are shown inTable 164. The case of angina in the BZA 20 mg/CE 0.625 group is discussed in SAEs above and the case in the BZA 20 mg/CE 0.45 group reportedly had cardiac origin ruled out. That subject also had acid reflux. No events of myocardial infarction were reported.

The data in Table 164 is most remarkable for chest pain and discomfort reported in the BZA 20 mg/CE 0.625 treatment group. Narratives for these subjects were reviewed. With the possible exception of the 48 year old woman discussed under SAEs above, none of these subjects were thought to have a cardiac origin of pain. It is likely that chest pain in various categories is more common in the BZA 20 mg/CE 0.625 treatment group than in the BZA 20 mg/CE 0.45 treatment group and other treatment groups by chance.

Table 164: Trial 306 Cardiac Disorders and Related Adverse Events Reported On- and Post-treatment

SOC Preferred term[2,3]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Chest discomfort	0	2 (1)	0	0	0.262
Chest pain	0	3 (1)	0	0	0.112
Non-cardiac chest pain	1 (<1)	3 (1)	0	0	0.321
Cardiac disorders	5 (2)	6 (3)	0	0	0.130
Angina pectoris	1 (<1)	1 (<1)	0	0	0.804
Arrhythmia	0	1 (<1)	0	0	0.574
Cardiac flutter	1 (<1)	0	0	0	0.577
Mitral valve prolapse	0	1 (<1)	0	0	0.574
Palpitations	2 (1)	2 (1)	0	0	0.577
Tachycardia	1 (<1)	1 (<1)	0	0	0.804

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Malignancy

A case of breast cancer was reported in a 59 year old woman in the BZA 20 mg/CE 0.45 treatment group found on Day 53 as discussed in SAEs above. As noted there, the study drug is unlikely to have been causative due to timing. In addition, a case of breast neoplasm was reported in the BZA 20 mg/CE 0.45 treatment group and another in the placebo treatment group, but both of these were benign. A squamous cell carcinoma of the skin developed on Day 61 in a 53 year old woman in the BZA 20 mg treatment group with a prior history of skin cancer as reported under SAEs. No uterine malignancies were reported.

Breast Disorders Reported as Adverse Events

Breast disorders reported as adverse events in Trial 306 are shown in Table 165. For most preferred terms, the number of subjects reporting is small for each treatment group and relatively balanced between groups. The breast cancer case is discussed in SAEs above. Breast enlargement showed increase in the BZA 20 mg treatment group, but only two subjects in that group reported that AE. Breast pain was reported by a few subjects in all groups on bazedoxifene or the combination drug, but not in placebo (4

subjects (2%) in the BZA 20 mg/CE 0.45 mg treatment group, 5 subjects (2%) in the BZA 20 mg/CE 0.625 mg treatment group, 2 subjects (2%) in the BZA 20 mg treatment group, and no subjects in the placebo group). That will be evaluated in other studies.

Table 165: Trial 306 Breast Disorders Reported as Adverse Events on and after Therapy

SOC Preferred term[2,3]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Breast cancer	1 (<1)	0	0	0	0.577
Breast cyst	0	1 (<1)	1 (1)	0	0.481
Breast discharge	1 (<1)	0	1 (1)	0	0.483
Breast engorgement	1 (<1)	0	0	0	0.577
Breast enlargement	0	0	2 (2)	0	0.020*
Breast mass	0	0	1 (1)	0	0.177
Breast neoplasm (benign)	1 (<1)	0	0	1 (1)	0.457
Breast pain	4 (2)	5 (2)	2 (2)	0	0.508
Breast swelling	1 (<1)	1 (<1)	0	0	0.804
Breast tenderness	2 (1)	1 (<1)	1 (1)	1 (1)	0.938
Galactorrhea	0	0	1 (1)	0	0.177
Nipple pain	0	1 (<1)	0	1 (1)	0.456
Retracted nipple	1 (<1)	0	0	0	0.577
Thelitis	1 (<1)	0	0	0	0.577

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Uterine disorders reported as adverse events

All uterine and vaginal adverse events reported in Trial 306 are shown inTable 166. Bleeding events are similarly distributed among treatment groups (any bleeding event 5 subjects (2%) in the BZA 20 mg/CE 0.45 mg treatment group, 5 subjects (2%) in the BZA 20 mg/CE 0.625 mg treatment group, 2 subjects (2%) in the BZA 20 mg treatment group, and 1 subject (1%) in the placebo group). For a discussion of vaginal discharge, vulvovaginal pruritis, and vulvovaginal burning see under Adverse Events above.

Transvaginal ultrasound was performed at Baseline and Week 12 and is discussed in uterine safety review (Section 6.4 of the main clinical review). Endometrial biopsy was performed for subjects with endometrial thickness greater than 4 mm at Week 12 and is also discussed in Dr. Willett's review.

Table 166: Trial 306 Uterine and Vaginal Disorders Reported as Adverse Events on and after Therapy

SOC Preferred term[2,3]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Any bleeding event	5 (2)	5 (2)	2 (2)	1 (1)	0.851
Metrorrhagia	0	1 (<1)	0	0	0.574
Uterine hemorrhage	2 (1)	0	0	0	0.265
Vaginal hemorrhage	3 (1)	4 (2)	2 (2)	1 (1)	0.927
Other uterine or vaginal event					
Adenexa uteri mass	0	0	1 (1)	0	0.177
Adenexa uteri pain	1 (<1)	1 (<1)	0	2 (2)	0.293
Cervical cyst	0	1 (<1)	0	0	0.574
Cervical polyp	0	0	0	1 (1)	0.157
Dysmenorrhea	1 (<1)	0	1 (1)	0	0.483
Dyspareunia	1 (<1)	2 (1)	0	1 (1)	0.730
Endometrial disorder	0	1 (<1)	0	0	0.574
Endometrial hypertrophy	1 (<1)	2 (1)	0	0	0.575
Genital burning	0	1 (<1)	0	0	0.574
Genital discharge	0	1 (<1)	0	0	0.574
Ovarian cyst	1 (<1)	3 (1)	0	1 (1)	0.525
Pelvic pain	1 (<1)	3 (1)	2 (2)	0	0.398
Uterine cyst	0	2 (1)	0	0	0.262
Uterine polyp	0	1 (<1)	1 (1)	0	0.481
Uterine spasm	2 (1)	3 (1)	0	1 (1)	0.678
Vaginal cyst	0	1 (<1)	0	0	0.574
Vaginal discharge	3 (1)	10 (5)	0	3 (3)	0.045*
Vaginal disorder	0	1 (<1)	1 (1)	0	0.481
Vaginal inflammation	0	1 (<1)	0	0	0.574
Vaginal odor	0	1 (<1)	1 (1)	1 (1)	0.562
Vulvovaginal burning	0	5 (2)	1 (1)	0	0.057
Vulvovaginal discomfort	1 (<1)	3 (1)	2 (2)	0	0.398
Vulvovaginal dryness	2 (1)	5 (2)	3 (3)	1 (1)	0.506
Vulvovaginal pain	2 (1)	3 (1)	0	0	0.426
Vulvovaginal pruritis	4 (2)	12 (6)	4 (4)	1 (1)	0.078

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Laboratory:

Laboratory Adverse Events

Relatively few laboratory findings were reported as adverse events in Trial 306 as noted in Table 167, with generally very few for any single preferred term. Fasting cholesterol; HDL, LDL, and VLDL cholesterol; and triglycerides, were obtained with chemistry at Screening and Weeks 4 and 12. Estrogen therapy has been associated with increased triglyceride levels, but that is not noted in this study (see also

Table). Bazedoxifene monotherapy has been associated with increased transaminases, but that is not noted in this study.

Table 167: Trial 306 Laboratory Events Reported as Adverse Events

SOC Preferred term[2,3]	BZA20/CE0.45 N=219	BZA20/CE0.625 N=218	BZA20 N=110	Placebo N=105	P-value[1]
	n (%)	n (%)	n (%)	n (%)	
Blood and lymph					
Anemia	0	1 (<1)	0	0	0.574
Endocrine					
Hypothyroid	1 (<1)	0	0	1 (1)	0.457
Investigations					
Bilirubin increased	0	0	1 (1)	0	0.177
Calcium decreased	0	1 (<1)	0	0	0.574
Cholesterol increased	1 (<1)	1 (<1)	0	0	0.804
Glucose decreased	0	0	1 (1)	0	0.177
Glucose increased	1 (<1)	0	0	0	0.577
Potassium increased	2 (1)	0	0	0	0.265
Triglycerides increased	1 (<1)	2 (1)	1 (1)	0	0.747
Uric acid increased	1 (<1)	0	1 (1)	0	0.483
Blood in urine	0	1 (<1)	1 (1)	0	0.481
Lipids increased	1 (<1)	0	0	0	0.577
LFT abnormal	1 (<1)	0	0	0	0.577
LDL increased	1 (<1)	0	0	0	0.577
Neutrophils decreased	0	0	1 (1)	0	0.177
Transaminases increased	1 (<1)	0	0	0	0.577
WBC decreased	1 (<1)	0	1 (1)	0	0.483
Metabolism & nutr. disorders					
Hypercholesterolemia	0	0	1 (1)	0	0.177
Hyperlipidemia	0	1 (<1)	0	0	0.574
Hypokalemia	0	1 (<1)	0	0	0.574
Renal and urinary					
Hematuria	0	2 (1)	1 (1)	0	0.395

Source: NDA022247, GSR 0007, 5.3.5.1 (Information request response)
* $p \leq 0.05$
1 P-value for Chi-square
2 MedDRA version 15.1
3 On treatment and to 15 days post-treatment

Marked Laboratory Abnormalities

Table 168 shows numbers of subjects with laboratory abnormalities predetermined to be of potential clinical significance where at least two subjects in a treatment group for a particular test were in the significant range. In no case did subjects in the test drug groups appear to have potentially significant lab results more commonly that subjects in the placebo group except for hyponatremia, where only two subjects in the BZA 20 mg group had on-therapy values < 130 mg/dL. As no subjects in the combination drug group developed hyponatremia, this was likely a chance occurrence.

Table 168: Trial 306 Subjects with On-therapy Lab Results of Potential Clinical Importance, (at least 2 Subjects in a Treatment Group)

Test	Range	BZA20/CE0.45 N=218[2]	BZA20/CE0.625 N=214[2]	BZA20 N=106[2]	Placebo N=101[2]	P-value[1]
		n (%)	n (%)	n (%)	n (%)	
Total		18 (8)	12 (6)	9 (8)	5 (5)	0.532
Sodium	<130 mEq/L	0	0	2 (2)	0	0.018*
Potassium	<3.1 mEq/L	1 (<1)	2 (1)	0	0	0.578
Uric acid	>7.3 mg/dL	2 (1)	1 (<1)	2 (2)	1 (1)	0.676
Total bili	>1.7 mg/dL	1 (<1)	1 (<1)	2 (2)	0	0.319
Alk. Phos.	>149 U/L	2 (1)	2 (1)	1 (1)	1 (1)	1.000
Cholesterol, fast	>260 mg/dL[3]	1 (<1)	2 (1)	0	1 (1)	0.728
Triglycerides, fast	>330 mg/dL	5 (2)	3 (1)	2 (2)	1 (1)	0.827

Source: Clinical Study Report 67466, Tables 10.9 and 10-10
* $p \leq 0.05$
1 P-value for Chi-square
2 Some denominators for particular labs were slightly lower
3 Also increase from baseline > 50 mg/dL

Of subjects with lab results of potential clinical importance, two subjects were found with clinically important laboratory changes. These changes are not likely to be associated with the study drug:

- A 58 year old woman in the BZA 20 mg/CE 0.45 mg treatment group developed AST and ALT greater than 3 times the upper limit of normal on Day 84. Alkaline phosphatase and bilirubin were normal. Work up showed hepatitis C. The subject completed the study.
- A 53 year old woman randomized to placebo entered the study with as hematocrit of 34.0% and hemoglobin of 10.6 g/dL. At 4 and 12 weeks these had fallen to 30.0% and 9.7 g/dL and then 29.1% and 9.0 g/dL. The subject was reportedly asymptomatic, did not experience bleeding, and completed the study. The investigator did not report the decrease in hematocrit or hemoglobin as an adverse event and no additional lab testing was reported.

Mean Change from Baseline

Estrogen therapy has been associated with elevation of HDL cholesterol and triglycerides. In this study, combined bazedoxifene/conjugated estrogen and bazedoxifene monotherapy were associated with mild mean decreases in total and LDL cholesterol from Baseline to Week 12 (total, -14 mg/dL for BZA 20 mg/CE 0.45 mg, -15 mg/dL for BZA 20 mg/CE 0.625 mg, -16 mg/dL for BZA 20 mg, -8 mg/dL for placebo; LDL, -17 mg/dL for BZA 20 mg/CE 0.45 mg, -18 mg/dL for BZA 20 mg/CE 0.625 mg, -15 mg/dL for BZA 20 mg, -6 mg/dL for placebo) and slight increases in triglycerides (11 mg/dL for BZA 20 mg/CE 0.45 mg, 13 mg/dL for BZA 20 mg/CE 0.625 mg, 6 mg/dL for BZA 20 mg, 1 mg/dL for placebo). HDL cholesterol was essentially unchanged. These changes are not likely to be clinically significant.

Bazedoxifene monotherapy has been associated with elevated transaminases. In this study, combined bazedoxifene/conjugated estrogen and bazedoxifene monotherapy were associated with slight mean decreases from Baseline to Week 12 in ALT (-2 U for BZA 20 mg/CE 0.45 mg, -3 U for BZA 20 mg/CE 0.625 mg, -2 U for BZA 20 mg, 1 U for placebo) but little change for AST. Alkaline phosphatase showed mild reduction (-6 U for BZA 20 mg/CE 0.45 mg, -9 U for BZA 20 mg/CE 0.625 mg, -6 U for BZA 20 mg, no change for placebo, perhaps antiresorptive effect for the active drug groups). Total bilirubin showed a reduction of -0.1 mg/dL in all treatment groups which probably was not clinically significant.

Both bazedoxifene/conjugated estrogen and bazedoxifene monotherapy were associated with slight mean decreases from Baseline to Week 12 in calcium (-0.3 mg/dL for both combination treatment groups, -0.2 mg/dL for BZA, and -0.1 for placebo) and phosphorus (-0.4 mg/dL for BZA 20 mg/CE 0.45 mg, -0.3 mg/dL for BZA 20 mg/CE 0.625 mg, -.0.2 mg/dL for BZA 20 mg, and -0.1 mg/dL for placebo).

No mean change from Baseline to Week 12 was noted for creatinine. No clinically significant change was noted for BUN.

Both bazedoxifene/conjugated estrogen and bazedoxifene monotherapy were associated with slight mean decreases in hemoglobin and hematocrit from Baseline to Week 12 (hemoglobin, -0.3 g/dL for BZA 20 mg/CE 0.45 mg, -0.3 g/dL for BZA 20 mg/CE 0.625 mg, -0.2 g/dL for BZA 20 mg, no change for placebo; hematocrit, -0.9% for BZA 20 mg/CE 0.45 mg, -0.9% for BZA 20 mg/CE 0.625 mg, -0.6% for BZA 20 mg, no change for placebo). These changes are not clinically significant.

Shifts

Shift tables for laboratory were not provided.

Vital Signs

A total of 7 subjects were reported as having AEs of hypertension during the study: 2 subjects (1%) in the BZA 20 mg/CE 0.45 mg treatment group, 3 subjects (1%) in the BZA 20 mg/CE 0.625 mg treatment group, 1 subject (1%) in the BZA 20 mg treatment group, and 1 subject (1%) in the placebo group. Estrogens have been reported to increase blood pressure in some patients, but that is not apparent for hypertension as an adverse event.

A potentially clinically important increase from baseline of systolic BP was defined as ≥ 20 mm Hg increase with absolute value of ≥ 160 mm Hg. This occurred on-therapy for 5 of 218 subjects (2%) in the BZA 20 mg/CE 0.45 mg treatment group, 3 of 215 subjects (1%) in the BZA 20 mg/CE 0.625 mg treatment group, none of 109 subjects in the BZA 20 mg treatment group, and 1 of 101 subjects (1%) in the placebo group. A clinically important increase from baseline of diastolic BP was defined as ≥ 15 mm Hg increase with absolute value ≥ 90 mm Hg. This occurred on-therapy for 3 subjects (1%) in the

BZA 20 mg/CE 0.45 mg treatment group, 4 subjects (2%) in the BZA 20 mg/CE 0.625 mg treatment group, 1 subject (1%) in the BZA 20 mg treatment group, and 5 subjects (5%) in the placebo group. Not all subjects with potentially clinically important increases of blood pressure were reported as adverse events.

Mean change in systolic and diastolic blood pressure over the 12 weeks of the study was small and not different from placebo. Systolic blood pressure changed by a mean of 1.2 mmHg in the BZA 20 mg/CE 0.45 mg treatment group, 0.3 mmHg in the BZA 20 mg/CE 0.625 mg treatment group, -0.9 mmHg in the BZA 20 mg treatment group, and -0.1 mmHg in the placebo group. Diastolic blood pressure changed by a mean of -0.3 mmHg in the BZA 20 mg/CE 0.45 mg treatment group, 0.2 mmHg in the BZA 20 mg/CE 0.625 mg treatment group, -0.6 mmHg in the BZA 20 mg treatment group, and 1.0 mmHg in the placebo group.

Significant blood pressure increase was not seen with the bazedoxifene/conjugated estrogen in this study.

Weight increased was reported as an adverse event in no subjects in the BZA 20 mg/CE 0.45 mg treatment group, 5 subjects (2%) in the BZA 20 mg/CE 0.625 mg treatment group, 1 subject (1%) in the BZA 20 mg treatment group, and no subjects in the placebo group. A single subject in the BZA 20 mg/CE 0.625 mg treatment group had a potentially clinically important weight gain of ≥ 15% and ≥ 25 pounds over the course of the study. Weight changed by a mean of 0.6 kg in the BZA 20 mg/CE 0.45 mg treatment group, 0.4 in the BZA 20 mg/CE 0.625 mg treatment group, -0.1 kg in the BZA 20 mg treatment group, and 0.6 kg in the placebo group. The BZA 20 mg treatment group weight increase was less than placebo.

Safety Conclusions

In this 12 week trial of 652 subjects (safety population) with two arms of active combination therapy against bazedoxifene monotherapy and placebo at a 2:2:1:1 ratio, both doses of bazedoxifene/conjugated estrogen and bazedoxifene monotherapy were well-tolerated. Treatment emergent adverse events occurred in similar percentages of subjects across treatment groups (164 subjects (75%) in the BZA 20 mg/CE 0.45 mg treatment group, 175 subjects (80%) in the BZA 20 mg/CE 0.625 mg treatment group, 90 subjects (82%) in the BZA 20 mg treatment group, and 75 subjects (71%) in the placebo group). No deaths were reported. A case of breast cancer was reported early in active therapy in the BZA 20 mg/CE 0.45 mg treatment group. No patterns of withdrawal for adverse events were associated with active therapy. No serious adverse events or common adverse events appeared associated with active therapy with the exception of a few reports of breast pain in all active treatment groups. A possible SAE of ischemic cardiac pain was reported in the BZA 20 mg/CE 0.625 mg treatment group. The preferred terms of vulvovaginal pruritis and burning and vaginal discharge were more common in the BZA 20 mg/CE 0.625 mg treatment group only, and this finding will be

evaluated in other studies. More abdominal distension was reported in the bazedoxifene monotherapy group.

With estrogens, stroke and venous thromboembolic disorders are a concern. None were reported in this trial.

See section 6.4 of main clinical review of uterine safety analysis.

With bazedoxifene monotherapy elevated transaminases have been found, but that was not apparent in this trial.

Study 304

Protocol 3115A1-304-WW: 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 (CSR-68285 – f irst year and CSR-73414 – second year extension).

Formulations B and C

It should be noted that two different formulations of bazedoxifene/conjugated estrogens were utilized in this study, Formulation B and Formulation C. Because of the (b) (4) evaluation of formulation B, minor changes were made, which became Formulation C and all subjects were switched to Formulation C for the remainder of the trial. However, during the conduct of trial 304, results from the bioequivalence study 1117 became available. It was found that the bioavailability of bazedoxifene in Formulation C was 18% lower than the bioavailability of bazedoxifene in Formulation A, which had been used in the phase 3 dose-finding trial 303. Formulation B was shown to be bioequivalent to Formulation A.

Incidence of Endometrial Hyperplasia: The first primary efficacy outcome was the incidence of endometrial hyperplasia in the efficacy evaluable population at Month 12. An evaluation was also conducted at Month 24 for the extension study. Biopsy samples were read as endometrial hyperplasia by at least one pathologist for 16 subjects (2 in the BZA 20/CE 0.45, 12 in the BZA 20 mg/CE 0.625 group, 2 in the CE 0.45/MPA 1.5 group, and none in the placebo group). For the study endpoint, the reading of endometrial hyperplasia was based on agreement of two of three pathologists' reading of the endometrial biopsy samples.

Trial 31151A-304-WW: Subjects with Endometrial Hyperplasia				
Test	**BZA 20 / CE0.45 N=361**	**BZA 20/ CE 0.625 N=349**	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
Year 1, Efficacy Evaluable				
N	261	(b) (4)	119	135
n (%)	0		0	0
95% CI, upper limit	1.14		2.49	2.19
Year 2, Efficacy Evaluable				
N	131	(b) (4)	66	79
n (%)	0		0	0
95% CI, upper limit	2.26		4.44	3.72
Source: Based on gyn medical officer review of cases				

Because of the reported difference in bioavailability of Formulation B and Formulation C, a review was conducted to evaluate the duration of each formulation used. All subjects began the trial on Formulation B, with an average number of days on Formulation B of 207 days and a range of 7 days to 367 days. During the second year of the trial, all subjects received Formulation C, which was noted to have an 18% lower bioavailability of bazedoxifene, raising a question regarding endometrial protection with the lower bazedoxifene exposure in Formulation C. Of the nine cases of endometrial hyperplasia identified, four cases were identified at the Year 1 biopsy, and the rest at the Year 2 biopsy. (b) (4) All subjects began the trial on Formulation B and were switched to Formulation C around 180 days, sometimes later. During Year 2, all subjects received Formulation C. (b) (4)

Table 169: Trial 304 Formualtion B/C Exposure in Patients with Endometrial Hyperplasia

Trial 31151A-304-WW: Formulation Exposure in Subjects with Endometrial Hyperplasia					
Subject Id	**Form B stop**	**Form C start**	**Form C stop**	**Days on Form C to Bx**	**Study Day of Bx**
BZA 20mg/CE 0.625mg					
(b) (4)					
Source: compiled by reviewer from Form BC dataset Bx - biopsy					

Events Rates

Safety event rates for Trial 304 are shown in Table 170 below. Treatment emergent adverse events occurred in similar percentages of subjects across treatment groups. Two deaths occurred and serious adverse events were reported in 5% of the population. The percentage of subjects withdrawn due to adverse events was numerically higher in the active control (CE 0.45/MPA 1.5) group.

Table 170: Trial 304 Safety Event Rates

Trial 31151A-304-WW: Safety Events				
	BZA 20 CE0.45 N=361	**BZA 20/ CE 0.625 N=349**	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Any TEAE	320 (89)	304 (87)	162 (91)	149 (87)
Deaths	0	0	1 (1)	1 (1)
SAE	22 (6)	19 (5)	7 (4)	7 (4)
Withdrawal for AE	39 (11)	37 (11)	30 (17)	20 (12)
Source: compiled by reviewer based on MeDRA 15.1 dataset				

Exposure

A total of 1061 subjects were enrolled in the study, randomized and took at least one dose of study drug. Compliance with study medication was assessed using pill count, diary cards and verbal information. As outlined in Table 171 below, in the first year of the trial, 25 (2%) subjects took less than 80% of their study medication. The rate of noncompliance was similar between all treatment groups. In the year 2 extension trial, 49 (9%) subjects were less than 80% compliant with their study medication. Numerically more subjects in the study drug and active control treatment groups were less than 80% compliant with medication (8-17%) when compared to placebo (5%).

Table 171: Trial 304 Exposure

Trial 31151A-304-WW: Exposure				
	BZA 20 CE0.45 N=361	**BZA 20/ CE 0.625 N=349**	**CE 0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Year 1, N	**361**	**349**	**179**	**172**
< 80% compliance	8 (2)	7 (2)	4 (2)	6 (3)
Year 2, Extension, N	**168**	**177**	**84**	**94**
< 80% compliance	15 (9)	15(8)	14 (17)	5 (5)
Source, CSR 68285 supportive table 15.11 ; CSR 73414, supportive table 15.14				

Formulations B and C: All subjects began the trial receiving Formulation B. The mean number of days on Formulation B was 207 days with a range of 7 days to 367 days for the BZA 20/CE 0.45 group and 209 days with a range of 1 day to 365 days for the BZA 20/CE 0.625 group. For Formulation C, the mean number of days on therapy was 255 days with a range of 0 days to 577 days for the BZA 20/CE 0.45 group and 272 days with a range of 0 day to 576 days for the BZA 20/CE 0.625 group. One hundred and thirty two subjects (69 in the BZA 20/CE 0.45 group and 63 in the BZA 20/CE 0.625 group) did not receive Formulation C during the trial. All subjects enrolled in the second year trial extension received Formulation C only.

Deaths

Two subject deaths were reported during the two years of trail 304. A 48 year-old woman receiving CE 0.45/MPA 1.5 died of an intentional drug overdose on study day 177, 89 days post therapy. A 51 year old woman receiving placebo died suddenly on study day 660, 125 days post therapy. In addition to the two reported deaths, a third subject enrolled in the trial died - a 52 year old woman receiving BZA 20/CE 0.625 was diagnosed with acute myeloblastic leukemia on study day 364. She discontinued study medication on study day 360 and died six months after her last dose of study medication.

Serious Adverse Events

As outlined in Table 172 below, 55 subjects reported serious adverse events during the on-therapy or follow-up periods of this two year trial. Most events were sporadic in occurrence. The System Organ Classes (SOC) with the highest number of subjects were Neoplasm (13 subjects), Injury (10 subjects), Gastrointestinal (6 subjects), and Reproductive (5 subjects).

Of the neoplasms reported, basal cell carcinoma was the most common, occurring in 4 subjects (3 in the BZA 20/CE 0.625 group and one subject in the CE 0.45/MPA 1.5 group) followed by malignant melanoma, found in 3 subjects (one in the BZA 20/CE 0.625 group and two in the placebo group) and squamous cell carcinoma of skin found in 3 subjects (one subject each in the BZA 20/CE 0.45, CE 0.45/MPA 1.5, and placebo groups). The rest of the neoplasms reported were individual events including lung adenocarcinoma (BZA 20/CE 0.45), acute myeloid leukemia (BZA 20/CE 0.625), tonsil cancer (BZA 20/CE 0.625), and benign ovarian germ cell teratoma (placebo).

In the Injury SOC, overdose was reported in four subjects (2 in the BZA 20/CE 0.45, one in the BZA 20/CE 0.625, and one in the CE 0.45/MPA 1.5 group). Three subjects reported fracture: two subjects with ankle fracture and one subject with tibial fracture, all in the BZA 20/CE 0.45 group. One subject in the placebo group did sustain a cervical vertebral and rib fracture as well as traumatic lung injury and concussion due to a traffic accident.

Table 172: Subjects Reporting Serious Adverse Events

Trial 31151A-304-WW: Subjects Reporting Serious Adverse Events				
	BZA 20 / CE0.45 N=361	**BZA 20/ CE 0.625 N=349**	**CE 0.45/ MPA 1.5 N=179**	**Placebo N=172**
SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any SAE	22 (6)	19 (5)	7 (4)	7 (4)
Blood and Lymphatic	0	1		
Cardiac	1	1		
Eye		1		
Gastrointestinal	1	3	1	1
General &Administrative		2		1
Hepatobiliary	1	2		1
Infections and Infestations	2	2		
Injury, Poisoning, Procedural	7	1	1	1
Investigations	1	1		
Musculoskeletal, Connective Tissue	1	1		1
Neoplasms	2	6	1	4
Nervous	1			
Psychiatric			3	

Trial 31151A-304-WW: Subjects Reporting Serious Adverse Events				
	BZA 20 / CE0.45 N=361	BZA 20/ CE 0.625 N=349	CE 0.45/ MPA 1.5 N=179	Placebo N=172
SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Renal and Urinary	2			
Reproductive and Breast	2	1	2	0
Respiratory, Thoracic, Mediastinal	1			1
Surgical and Medical Procedures	1			
Vascular	3			
Source: compiled by reviewer based on MeDRA 15.1 data				

Adverse Events Leading to Withdrawal

As outlined in Table 173 below, 126 (12%) subjects withdrew from trial 304 because of adverse events. Musculoskeletal adverse events accounted for the largest number of events. An imbalance is noted in the Reproductive SOC, where 19 subjects (11%) in the CE 0.45/MPA 1.5 group withdrew compared to 1 – 3% subjects in the other treatment groups.

Table 173: Subjects Withdrawing due to Adverse Events

Trial 31151A-304-WW: Subjects Withdrawing due to Adverse Events				
	BZA 20 / CE0.45 N=361	BZA 20/ CE 0.625 N=349	CE 0.45/ MPA 1.5 N=179	Placebo N=172
SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AE leading to withdraw	39 (11)	37 (11)	30 (17)	20 (12)
Blood and Lymphatic	0	0	1 (1)	0
Cardiac	3 (1)	1 (1)	2 (1)	1 (1)
Eye	1 (1)	1 (1)	0	0
Gastrointestinal	4 (1)	7 (2)	2 (1)	1 (1)
General &Administrative	3 (1)	1 (1)	1 (1)	1 (1)
Hepatobiliary	1 (1)	0	0	0
Infections and Infestations	4 (1)	0	0	2 (1)
Injury, Poisoning, Procedural	0	1 (1)	0	0
Investigations	4 (1)	1 (1)	3 (1)	3 (2)
Metabolism and Nutrition	0	0	0	1 (1)
Musculoskeletal, Connective Tissue	10 (3)	8 (2)	4 (2)	6 (4)
Neoplasms	0	2 (1)	0	2 (1)
Nervous	4 (1)	3 (1)	0	0
Psychiatric	2 (1)	2 (1)	2 (1)	0

Trial 31151A-304-WW: Subjects Withdrawing due to Adverse Events				
	BZA 20 / CE0.45 N=361	BZA 20/ CE 0.625 N=349	CE 0.45/ MPA 1.5 N=179	Placebo N=172
SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Renal and Urinary	1 (1)	0	0	0
Reproductive and Breast	3 (1)	9 (3)	19 (11)	2 (1)
Respiratory, Thoracic, Mediastinal				
Skin and Subcutaneous	4 (1)	1 (1)	1 (1)	1 (1)
Surgical and Medical Procedures				
Vascular	6 (2)	3 (1)	0	2 (1)
Source: CSR73414, supportive table 15.51				

Adverse Events Leading to Dose Alteration

No other adverse events were found to have led to study drug discontinuation or dose reduction.

Adverse Events

On- and post-treatment adverse events for Trial 304 are shown in the Table 174 below. Totals differ from Table 170 as AEs in the 15 day post-treatment period are included. The SOCs with the highest number of subjects reporting events were Infections and Infestations, Musculoskeletal, Connective Tissue, Gastrointestinal, and Nervous. Most common reported adverse events were headache, nasopharyngitis, back pain, and arthralgia.

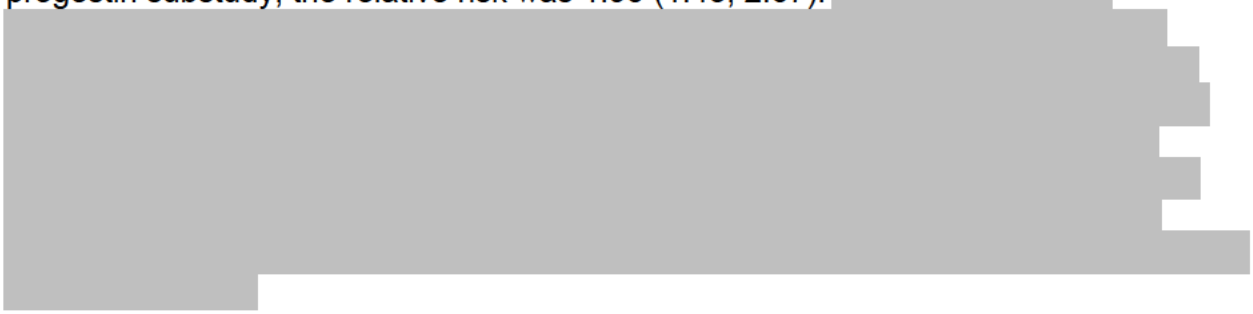
Table 174: Trial 304 Subjects Reporting Adverse Events On-Therapy or Post-Therapy

Trial 31151A-304-WW: Subjects Reporting Adverse Events On-Therapy or Post-Therapy				
SOC ***PT***	**BZA 20 / CE0.45 N=361**	**BZA 20/ CE 0.625 N=349**	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Any AE	**320 (89)**	**305 (87)**	**162 (91)**	**149 (87)**
Blood and Lymphatic	8 (2)	9 (3)	4 (2)	5 (3)
Cardiac	17 (5)	3 (1)	6 (3)	6 (3)
Congenital, familial, genetic	0	0	2 (1)	0
Ear and labyrinth	9 (2)	16 (5)	6 (3)	7 (4)
Endocrine	4 (1)	3 (1)	2 (1)	4 (2)
Eye	13 (4)	20 (6)	8 (4)	12 (7)
Gastrointestinal	126 (35)	138 (40)	72 (40)	56 (33)

Trial 31151A-304-WW: Subjects Reporting Adverse Events On-Therapy or Post-Therapy				
SOC ***PT***	**BZA 20 / CE0.45 N=361**	**BZA 20/ CE 0.625 N=349**	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Abdominal pain, upper	*28 (8)*	*18 (4)*	*11 (6)*	*4 (2)*
General &Administrative	61 (17)	66 (19)	31 (17)	34 (20)
Hepatobiliary	6 (2)	4 (1)	0	2 (1)
Immune system	21 (6)	17 (5)	9 (5)	9 (5)
Infections and Infestations	198 (55)	187 (54)	103 (58)	84 (49)
Nasopharyngitis	*72 (20)*	*77 (22)*	*40 (22)*	*28 (16)*
Influenza	*39 (11)*	*32 (9)*	*23 (13)*	*14 (8)*
Upper respiratory infection	*28 (8)*	*33 (9)*	*13 (7)*	*11 (6)*
Sinusitis	*28 (8)*	*20 (6)*	*7 (4)*	*13 (8)*
Injury, Poisoning, Procedural	69 (19)	81 (23)	30 (17)	37 (22)
Investigations	45 (12)	33 (9)	22 (12)	19 (11)
Metabolism and Nutrition	17 (5)	15 (4)	11 (6)	20 (12)
Musculoskeletal, Connective Tissue	158 (44)	164 (47)	69 (39)	79 (46)
Back pain	*51 (14)*	*59 (17)*	*28 (16)*	*20 (12)*
Arthralgia	*52 (14)*	*48 (14)*	*20 (11)*	*26 (15)*
Pain in extremity	*37 (10)*	*37 (11)*	*16 (9)*	*24 (14)*
Muscle spasms	*36 (10)*	*28 (8)*	*16 (9)*	*10 (6)*
Myalgia	*34 (9)*	*24 (7)*	*14 (8)*	*16 (9)*
Neoplasms	14 (4)	13 (4)	5 (3)	8 (5)
Nervous	111 (31)	106 (30)	66 (37)	47 (27)
Headache	*84 (23)*	*68 (19)*	*51 (28)*	*35 (20)*
Psychiatric	40 (11)	33 (9)	32 (18)	27 (16)
Renal and Urinary	19 (5)	12 (3)	13 (7)	9 (5)
Reproductive and Breast	89 (25)	86 (25)	79 (44)	35 (20)
Respiratory, Thoracic, Mediastinal	64 (18)	57 (16)	34 (19)	33 (19)
Skin and Subcutaneous	53 (15)	57 (16)	31 (17)	26 (15)
Surgical and Medical Procedures	3 (1)	3 (1)	0	1 (1)
Vascular	52 (14)	53 (15)	16 (9)	15 (9)
Hot flush	*37 (10)*	*35 (10)*	*10 (6)*	*7 (5)*
Vaginal hemorrhage	*19 (5)*	*27 (8)*	*32 (18)*	*7 (5)*
Source: compiled by reviewer based on MeDRA 15.1 data				

Adverse Events of Special Interest

Venous thromboembolism (VTE): Venous thromboembolism is a known adverse reaction for both estrogen and estrogen agonist/antagonists. In the Women's Health Initiative (WHI) estrogen alone substudy, the relative risk (95% CI) of deep venous thrombosis for conjugated estrogens was 1.47 (1.06, 2.06). For the estrogen plus progestin substudy, the relative risk was 1.95 (1.43, 2.67). (b) (4)



Cerebrovascular events: In a trial of postmenopausal women with documented coronary artery disease, an increased risk of death due to stroke was observed during treatment with an estrogen agonist/antagonist. In the WHI estrogen-only substudy, and increased risk of stroke was observed. (b) (4)

Cardiovascular events: In the WHI estrogen plus progestin substudy, there was an increased risk of coronary artery disease events compared to placebo. No overall difference was seen the in the WHI estrogen-only substudy. No overall difference in cardiovascular events was seen the in the bazedoxifene monotherapy trial 301. Over the two years of trial 304, coronary artery disease events were reported in four subjects (2 in the BZA 20/CE 0.45, one in the BZA 20 mg/CE 0.625 group, and one in the CE 0.45/MPA 1.5 group). One subject in the BZA 20/CE 0.45 group suffered a myocardial infarction on study day 701. Cardiac evaluations were conducted in 53 subjects (17 in the BZA 20/CE 0.45, 16 in the BZA 20 mg/CE 0.625 group, 11 in the CE 0.45/MPA 1.5 group, and 9 in the placebo group). Invasive cardiac evaluations were conducted in five subjects (2 in the BZA 20/CE 0.45, 2 in the BZA 20 mg/CE 0.625 group, and one in the placebo group).

Neoplasms: During the two years of trial 304, 40 subjects reported at least one neoplasm adverse event (14 in the BZA 20/CE 0.45, 13 in the BZA 20 mg/CE 0.625 group, 5 in the CE 0.45/MPA 1.5 group, and 8 in the placebo group). The most commonly reported event was uterine leiomyoma, reported in 16 subjects with more reports in the bazedoxifene/estrogen groups (7 in the BZA 20/CE 0.45, 5 in the BZA 20

mg/CE 0.625 group, 2 in the CE 0.45/MPA 1.5 group, and 2 in the placebo group). Reported malignant neoplasms were predominantly of skin origin – malignant melanoma (3 subjects), basal cell carcinoma (5 subjects), and squamous cell carcinoma of the skin (3 subjects).

Reproductive disorders: Reproductive tissues are the prime target for both estrogens and estrogen agonist/antagonists. Adverse events relating to the breast were reported by 95 subjects (31 in the BZA 20/CE 0.45, 24 in the BZA 20 mg/CE 0.625 group, 29 in the CE 0.45/MPA 1.5 group, and 11 in the placebo group) [Table 175]. The most common adverse event was breast or nipple pain, discomfort or tenderness which was reported by 25 subjects in the BZA 20/CE 0.45, 22 subjects in the BZA 20 mg/CE 0.625 group, 23 subjects in the CE 0.45/MPA 1.5 group, and 6 subjects in the placebo group. Beast mass was reported by three subjects (one in the BZA 20 mg/CE 0.625 group and 2 in the CE 0.45/MPA 1.5 group). Fibrocystic breast disease and related changes (i.e., mammarian dysplasia) was reported by eight subjects (4 in the BZA 20/CE 0.45, 2 in the BZA 20 mg/CE 0.625 group, one in the CE 0.45/MPA 1.5 group, and one in the placebo group). No reports of breast malignancy were reported in the trial.

Adverse reactions relating to the ovaries and fallopian tubes we reported by 15 subjects (6 in the BZA 20/CE 0.45, one in the BZA 20 mg/CE 0.625 group, 3 in the CE 0.45/MPA 1.5 group, and 3 in the placebo group) during the two years of the trial. The most commonly reported events were ovarian cyst, ovarian mass, and ovarian pain. One benign ovarian germ cell teratoma was reported in a placebo-treated subject.

Adverse reactions relating to the uterus, vulva, or vagina were reported by 211 subjects (57 in the BZA 20/CE 0.45, 71 in the BZA 20 mg/CE 0.625 group, 63 in the CE 0.45/MPA 1.5 group, and 20 in the placebo group). (b) (4)

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Mammogram

Mammography evaluations were conducted at screening and month 12. For the second year extension, 423 of the enrolled 523 subjects had mammography at month 24. Clinically important abnormal mammography results were identified in 11 subjects (2 in the BZA 20/CE 0.45, 3 in the BZA 20 mg/CE 0.625 group, 2 in the CE 0.45/MPA 1.5 group, and 4 in the placebo group). The abnormal readings were predominantly Bi-Rads 3 or 4. Biopsy results, when performed, were negative.

Laboratory:

Laboratory Adverse Events

Laboratory adverse events were reported by 46 subjects. The most common adverse events reported were blood cholesterol increased and blood triglycerides increased.

Marked Laboratory Abnormalities: The Applicant utilized predetermined laboratory values of potential clinical importance to identify subjects for further review, including laboratory results, vital sing measurements, adverse event records and any other pertinent sections of the CRF and correspondence. Prior to data unblinding, a decision was then made regarding the clinical impotence of the laboratory abnormality. As outlined in the table below, clinically important laboratory findings were identified in 8 subjects, predominantly elevation of total cholesterol or triglycerides or both. Estrogens are known to cause increases in triglyceride levels.

Table 178: Trial 304 Subjects with Clinically Important Labs

Trial 31151A-304-WW: Subjects with Clinically Important Labs				
Test	**BZA 20 CE0.45 N=361**	**BZA 20 CE 0.625 N=349**	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Total	3 (1)	2 (1)	2 (1)	1 (1)
Hematocrit	0	1 (<1)	0	0
SGOT ALT	0	0	1 (1)	0
Total Cholesterol	0	1 (<1)	0	1 (1)
Triglycerides	3 (1)	1 (<1)	1 (1)	0
Source: CSR 73414, table 15.54				

Mean Change from Baseline: Mean changes in laboratory values at months 6, 12, and 24 were reviewed. No clinically important mean changes in laboratory values were noted.

Vital Signs

Across the two year study, clinically important changes in vital signs (increased systolic blood pressure, diastolic blood pressure, or both) were noted in 10 subjects (4 in the BZA 20/CE 0.45, 2 in the BZA 20 mg/CE 0.625 group, 4 in the CE 0.45/MPA 1.5 group, and none in the placebo group). No subjects were withdrawn from the study due to vital sign changes.

Electrocardiograms

Electrocardiograms (ECGs) were collected at baseline, month 12, and month 24. ECGs were collected on 861/1061 (81%) subjects in the safety population. Over the two years of the study, 16 subjects had abnormal ECG findings of potential clinical importance (7 in the BZA 20/CE 0.45, 4 in the BZA 20 mg/CE 0.625 group, 3 in the CE 0.45/MPA 1.5 group, and 2 in the placebo group). These subjects records were further reviewed in a blinded manner. Overall, five subjects were found to have clinically important ECG changes.

- A 53yo receiving BZA 20/CE 0.45 was noted to have abnormal t wave changes on the month 24 ECG. No abnormalities were noted on nuclear stress test.
- A 51yo receiving BZA 20/CE 0.45 was noted to have first degree AV block and bradycardia on the month 24 ECG. No abnormalities were on stress test or echocardiogram.
- A 53yo receiving BZA 20/CE 0.45 was noted to have ST-T wave abnormalities and possible left ventricular hypertrophy on the month 12 ECG. The subject was referred to her primary care physician and no further evaluation was done.

- A 54yo receiving BZA 20 mg/CE 0.625 was noted to have a possible old infarct on month 24 ECG. Work-up was negative.
- A 52yo receiving CE 0.45/MPA 1.5 was noted to have sinus bradycardia and ST-T wave changes at month 12. Work-up was negative for ischemic disease.

Safety Conclusions

The safety profile of the bazedoxifene/conjugated estrogen combination product is similar to the known safety profile of estrogen and estrogen agonist/antagonist products.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARCEA B WHITAKER
06/05/2013

GERALD D WILLETT
06/05/2013

STEPHEN R BIENZ
06/05/2013

STEPHEN R VOSS
06/05/2013

THERESA E KEHOE
06/05/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 022247 **Applicant: Pfizer/Wyeth** **Submission Date: October 3, 2012**

Drug Name: Pending (proposed-(b) (4)) **NDA/BLA Type: 505(b)(1) Standard Review**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			There is a written report for both ISS and SCS along with numerous supportive tables (Module 5.3.5.3.28)
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			There is a written report for both ISE and SCS along with numerous supportive tables (Module 5.3.5.3.27)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Benefit and risk conclusions are presented in the Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product	X			The LED may be a review issue.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

	Content Parameter	Yes	No	NA	Comment
	(*i.e.*, appropriately designed dose-ranging studies)? On several occasions (tcon minutes 12/4/2001, division letter 6/4/2004 and SPA 1/13/2005), the Division advised the sponsor to identify the lowest effective dose (LED). The phase 2 dose-finding study (203) used two CE doses (0.3 and 0.625) and 3 BZA doses (5, 10, 20 mg). • For endometrial safety, the LED for BZA was deemed to be 20 mg. (b) (4) [redacted] • For VMS, in the phase 2 study, CE 0.625 showed a reduction in hot flushes at all BZA doses (5, 10, 20). The 0.3 dose only showed a reduction at BZA 5 mg. The CE 0.45 dose, which was not evaluated in Phase 2, was compared to 0.625 in study 303 and 305. Two dose regimens (0.625/20 and 0.45/20) are being sought by the sponsor for VMS. • For VVA, only vaginal maturation was assessed in Phase 2. (b) (4) [redacted] In Study 306, 0.625/20 and 0.45/20 doses were compared. Only the 0.625/20 dose is being proposed by the sponsor for the VVA indication. Dose groups in Study 303 were amended to add a lower BZA arm (0.625/10 mg). In meeting minutes dated 8/23/2005, the sponsor asked if the agency concurred with 0.625/20 mg BZA and 0.45 CE/20 mg BZA were appropriate doses to include in studies 304, 305 and 306. The response was "yes" which suggests that the Division felt adequate dose finding had been accomplished.				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1 (303):** A 2-year double-blind, randomized, Placebo- and active-controlled study in postmenopausal women Primary endpoints: endometrial hyperplasia at 12 months/lumbar spine BMD at 24 months Secondary endpoints: hot flushes (number and severity), vag.maturation index Indications: Prevention of Postmenopausal Osteoporosis (PMO), Vasomotor Symptoms (VMS), ~~Vulva and Vaginal Atrophy (VVA)~~ **Pivotal Study #2 (3307):** A 1-year double-blind,	X			• Study 303 will not be a pivotal study in support the VVA indication since only one of the 3 necessary components was measured. Based on guidance given on 10/9/2001, a 12-week study for VVA would be sufficient (fulfilled with Study 306). • Study 303 VMS

	Content Parameter	Yes	No	NA	Comment
	randomized, placebo- and active-controlled study in postmenopausal women Primary endpoints: endometrial hyperplasia at 12 months/lumbar spine BMD at 12 months Indication: Prevention of Postmenopausal Osteoporosis **Pivotal Study #3 (305):** A 12-week double-blind, randomized, placebo-controlled study for the treatment of vasomotor symptoms in postmenopausal women Primary endpoint: hot flush frequency/severity at 4 and 12 weeks Indication: VMS **Pivotal Study #4 (306):** A 12-week double-blind, randomized, placebo- and active-controlled study of mod/severe vulvar/vaginal atrophy in postmenopausal women Co-Primary endpoints: most bothersome symptom, vag pH, vaginal maturation index Indication: VVA				population is small and may not qualify as a pivotal study. One study is likely sufficient (fulfilled with Study 305). • In a letter dated 4/13/2005, the sponsor asked the Agency if 303, 304, 305 and 306 to support clinical requirement. DRUP responded "yes" for efficacy. The safety answer was more complex.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			An active control using the CE dose in the combo product was requested by the Division in the osteoporosis study.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			All primary endpoints were agreed upon. Issues with secondary endpoints are outlined above.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? From Clinical Overview: "The majority of the patients were from the US and South America, although some subjects were enrolled in the EU. "…The patient population studied was reflective of the population for whom BZA/CE will be prescribed in all regions studied."	X			• 68% (4380/6426) of subjects in the 4 pivotal studies were from the US. • For the South American study 304, the study had to enroll 80% US patients. Study 3307, the replacement to 304 enrolled 3860 of 4774 (80%) subjects from the US (demowder.xpt)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval	X			Information is available for BZA

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	studies, if needed)?				alone (b) (4) [redacted] (no effects at 20 mg and 120 mg) No evidence in the literature for CE effects on QT. No ECG evidence from combination product studies of prolonged QT.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			(b) (4) [redacted]
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		Additionally they have used multiple versions of MedDRA with this submission which makes the integrated analysis difficult to interpret
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? The sponsor has submitted the following: • (b) (4) [redacted]	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	(b) (4) • Two endometrial safety studies have been submitted • An active control comparator using the same CE dose as proposed to be marketed for the osteoporosis prevention indication was submitted • Formal QT study was submitted and reviewed (b) (4) and will be sufficient for this NDA • Separate ISS for the 12-week studies supporting the VMS/VVA indications (Studies 305 and 306) in supportive tables (5.3.5.3.28)				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			See explanation #17
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			SAS datasets and CDISC format for Phase 3 studies of BZA/CE
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?		X		See MedDRA comment above.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			Per statistical reviewers
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			CRFs and datasets have not been submitted for Phase 1 or 2 studies using BZA monotherapy (b) (4)
37.	Has the applicant submitted all additional Case Report	X			CRFs have been

	Content Parameter	Yes	No	NA	Comment
	Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				submitted for all subjects who underwent clinical evaluation for possible venous or arterial disease regardless testing outcome.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			113 investigators had financial information to disclose. 105 investigators had significant payments of other sorts to disclose and 8 investigators had equity in the sponsor to disclose.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __X_Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

1. The satisfactory submission of the updated datasets with adverse events recoded in a single MedDRA dictionary and updated integrated tables for the Phase 3 studies may be a filing issue. The following comment was communicated to the Applicant on 11/6/2012:

   We are reviewing the application and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

   We note that multiple different versions of MedDRA have been used for coding adverse events for basedoxifene/CEE studies and bazedoxifene monotherapy studies. This approach significantly inhibits our ability to conduct standardized MedDRA queries in our review of the safety of your bazedoxifene/CEE product. As outlined in the attached memo from the MedDRA Maintenance and Support System Organization (MSSO), the reports in a project should all be coded with the same version of MedDRA and preferably, the most recent version of MedDRA.

   We request that you re-submit the safety databases for all bazedoxifene/CEE studies, the bazedoxifene/CEE integrated summary of safety, bazedoxifene monotherapy studies, and the bazedoxifene monotherapy integrated summary of safety using a single MedDRA version, preferably the most recent version of MedDRA. Please provide a timeline for this submission by 11/12/2012.

   If recoding of the safety databases cannot be conducted in a timely manner, justify the impact of the various versions of MedDRA and clearly outline for each study which version of MedDRA was used and which MedDRA preferred terms are

coded in multiple System Organ Classes (SOCs) based on the different MedDRA versions.

At this time, the applicant has agreed to submit the updated datasets recoded to MedDRA 15.1 and the updated integrated tables by 11/30/2012.

Please identify and list any potential review issues –**Internal Comments**

(b) (4)

Please identify and list any potential review **issues to be forwarded to the Applicant for the 74-day letter.**

None.

Due to prior agreements between the Applicant and the Division, the above potential review issues should not be conveyed to the sponsor until a substantive review of the application has occurred.

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARCEA B WHITAKER
11/21/2012

GERALD D WILLETT
11/27/2012

THERESA E KEHOE
11/28/2012