CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022247Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 3, 2013

FROM: Julie Beitz, MD

SUBJECT: Approval Action for NDA 022247/Original 1
Duavee (conjugated estrogens 0.45 mg/bazedoxifene 20 mg)
Treatment of vasomotor symptoms
Prevention of postmenopausal osteoporosis

Complete Response Action for NDA 022247/Original 2
Duavee (conjugated estrogens 0.625 mg/bazedoxifene 20 mg)
Treatment of vulvar and vaginal atrophy
Treatment of vasomotor symptoms
Prevention of postmenopausal osteoporosis

Wyeth Pharmaceuticals, Inc.

Summary

Duavee (conjugated estrogens/bazedoxifene, hereafter referred to as CE/BZA) pairs conjugated estrogens (i.e., Premarin) with bazedoxifine. Conjugated estrogens are composed of multiple estrogens that demonstrate estrogen receptor agonist activity.[1] Bazedoxifene, a new molecular entity, demonstrates both tissue selective estrogen receptor agonist and antagonist activity. The CE/BZA combination is not currently approved in any country.

Bazedoxifene monotherapy is not currently FDA-approved. Bazedoxifene is approved in Europe (as Conbriza 20 mg) and in other countries, including Japan, for the treatment of osteoporosis. Studies using BZA monotherapy for the treatment and prevention of postmenopausal osteoporosis were previously reviewed (b) (4) Bazedoxifene monotherapy has been shown to have beneficial effects on bone mineral density and to reduce fracture risk (b) (4)

Conjugated estrogens combined with BZA have net estrogen agonist activity in bone, although increasing BZA doses mitigate the effects of CE in bone. In the uterus, BZA appears to act as an estrogen antagonist and opposes the effect of CE.

The applicant submitted NDA 022247 on October 3, 2012 seeking approval for CE/BZA for three indications: treatment of moderate to severe vasomotor symptoms associated with postmenopause (VMS), treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause (VVA), and prevention of post-menopausal osteoporosis (PMO). For the VMS and PMO indications, the applicant has proposed two doses: CE 0.45/BZA 20 and CE 0.625/BZA 20. For VVA, the applicant has proposed only the CE 0.625/BZA 20 dose.

The Division of Bone, Reproductive and Urologic Products (DBRUP) has concluded that the benefits of CE 0.45/BZA 20 for 1) treatment of moderate to severe vasomotor symptoms in postmenopausal women with a uterus and 2) prevention of postmenopausal osteoporosis in women with a uterus outweigh the potential risks, and has recommended approval of this dose for these indications.

[1] Conjugated estrogens are purified from pregnant mares' urine and consist of the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine.

Reference ID: 3383786

In addition, the Division has raised the following concerns that preclude approval of CE 0.625/BZA 20 for any indication at this time:

(b) (4)

This memo documents my concurrence with these conclusions and recommendations. NDA 022247 has been administratively split as follows:

- Original 1 will contain information supporting the use of CE 0.45/BZA 20 for the VMS and PMO indications while,

- Original 2 will contain information supporting the use of CE 0.625/BZA 20 the VVA, VMS and PMO indications.

Discussions regarding product labeling and postmarketing requirements have been satisfactorily completed and there are no inspectional issues that preclude approval of NDA 022247/Original 1 for CE 0.45/BZA 20 for the VMS and PMO indications. NDA 022247/Original 2 for CE 0.625/BZA 20 supporting the VVA, VMS and PMO indications will receive a Complete Response action.

Regulatory History

Evaluation of the combination of CE and BZA has been conducted (b) (4) under IND 062288 (treatment of vasomotor symptoms, and vulvar and vaginal atrophy, Division of Reproductive and Urologic Products).

On July 18, 2007, a pre-NDA meeting was held jointly with the two review divisions. At that meeting it became apparent that Study 304, supporting the PMO indication and endometrial protection claim, utilized a drug product formulation that was not bioequivalent to the formulation used in another phase 3 trial supporting the PMO indication (Study 303), and that an unacceptable rate of endometrial hyperplasia was observed.

A Type C meeting was held on February 12, 2008, to discuss product quality, clinical pharmacology, and clinical issues related to formulation changes that occurred during development. At that meeting, FDA noted that based on the available data (b) (4) 2) that endometrial protection had been demonstrated for CE 0.45/BZA 20 (b) (4) (b) (4).

The applicant submitted a new trial supporting the PMO indication and endometrial protection claim (Study 3307) under a Special Protocol Assessment request in August 2008. Agreement was reached that Study 3307 would be an acceptable replacement for Study 304.

On October 27, 2008, IND (b) (4) was transferred to the Division of Reproductive and Urologic Products (later renamed DBRUP).

On February 17, 2010, the Division provided written comments to Wyeth regarding the results of bioequivalence studies conducted to demonstrate bridging of the to-be-marketed CE/BZA tablet formulation with clinical Formulations A and B used in the phase 3 trials. The Division also provided preliminary comments for a pre-NDA meeting scheduled for September 26, 2011; the sponsor cancelled the meeting following receipt of the comments.

In January 2012, Wyeth requested a Type C meeting with the Division and the Office of Scientific Investigations (OSI). Following review of the meeting package submitted on March 30, 2012, OSI requested additional information regarding monitoring procedures during the conduct of the clinical trials, methods used to select sites for third party audits, the extent of missing source documents at various sites, and the impact of audit findings on the trial results. Wyeth provided the requested information in May and June 2012. After reviewing this information, OSI provided additional comments to Wyeth on September 11, 2012, requesting that the NDA submission contain: 1) a tabular accounting of the availability of source documentation for all investigational sites enrolling subjects in each trial, 2) information regarding monitoring and oversight of each trial, and 3) third party audit reports for the phase 3 trials. At a meeting held on September 14, 2012, the sponsor agreed to submit this information.

NDA 022247 was received on October 3, 2012, and reviewed in accordance with timelines specified in The Program. The application was granted a standard 12-month review. Information regarding missing source documents was received on February 19, 2013. The Late-Cycle Meeting (LCM) was held on June 26, 2013. An advisory committee meeting was not held because outside expertise was not deemed necessary.

Product Quality Considerations

(b) (4)

The following substantive review issues were raised at the LCM with the applicant, and subsequently addressed during the review:

1) (b) (4) dissolution failures were discovered during FDA's drug product manufacturing site inspection. Additional information is required to determine how the (b) (4) phenomenon (b) (4) will affect the quality of the proposed to-be-marketed drug product and support use of the data from the primary stability batches to set an expiration dating period.

The applicant stated that the (b) (4) issue can be mitigated (b) (4) Release testing and 3-month stability data on confirmatory batches were submitted on July 31, 2013, and met acceptance criteria for both CE and BZA dissolution. (b) (4) Thus, the Agency's concerns were adequately addressed.

2) Environmental Assessments (EA) for CE and BZA have not been submitted. The applicant was advised to submit an EA for BZA; the EA for conjugated estrogens could be literature-based using data available on estrogens, estradiol equivalents and exposure models to assess the risks to ecological species. The applicant agreed to provide the requisite EAs, but without information on estradiol, by July 31, 2013. The applicant also proposed to provide additional CE information from GLP study reports on March 31, 2015. On July 3, 2013, the applicant submitted the proposed content for its EAs which was found acceptable. Review of the EAs submitted on July 31, 2013 found that approval of CE/BZA is not expected to have a significant impact on the human environment. Thus, the Agency's concerns were adequately addressed.

3) A test and acceptance criterion for [redacted] (b) (4) bazedoxifene in the drug product is needed. The applicant's June 4, 2012 amendment adequately addressed this request.

Inspections of manufacturing facilities were conducted; on August 14, 2013, the Office of Compliance determined the facilities to be acceptable.

Clinical Pharmacology

After administration of a single dose of CE/BZA, baseline-adjusted total estrone (representing CE) is eliminated with a half life of approximately 17 hours. Bazedoxifene is eliminated with a half life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration.

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. In postmenopausal women, a significant proportion of circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

The metabolic disposition of BZA has been determined following oral administration of 20 mg of radiolabeled bazedoxifene. Bazedoxifene is extensively metabolized; glucuronidation is the major metabolic pathway.

Drug interactions. *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by CYP3A4. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort 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 an increased risk for endometrial hyperplasia.

Bazedoxifene undergoes little or no CYP P450-mediated metabolism and does not induce or inhibit the activities of major CYP isoenzymes. *In vitro* data suggest that BZA is unlikely to interact with co-administered drugs via CYP-mediated metabolism. Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver. The metabolism of BZA may be increased by concomitant use of substances known to induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin. A reduction in BZA exposure may be associated with an increased risk of endometrial hyperplasia.

Because of the potential for loss of uterine protection when exposures to conjugated estrogens increase relative to exposures to bazedoxifine , the applicant will be required to conduct a drug-drug interaction trial post-approval to characterize the pharmacokinetic profile of conjugated estrogens when co-administered with a strong CYP3A4 inhibitor.

Formulation changes. Over the 10-year period of drug development, several formulation changes occurred. Formulation A (the original formulation) was used in Study 303 (PMO indication). Formulation B was used in Study 305 (VMS indication) and Study 306 (VVA indication). Study 304 used both Formulations B and C, however the BZA component of Formulation C was found to be 18% less bioavailable than the BZA component of Formulation A. In a written response dated October 10, 2008, to a Special Protocol Assessment, the Division agreed that Study 3307, which used Formulation A, could replace Study 304 in support of the PMO indication and endometrial protection claim.

Effect of body weight. The Agency's population PK analysis of dense PK data found that BZA clearance increased with body weight. Subjects over 75 kg were observed to have an average clearance that was 17% higher than those with lower body weight (less than or equal to 75 kg). Accordingly, a 17% decrease in BZA exposure is expected in this group of women. This decrease in BZA exposure could result in loss of endometrial protection.

QT Assessment. In a thorough QT study that evaluated up to 120 mg of BZA, no QTc prolongation was observed.

Pediatric Use. The pharmacokinetic profile of CE/BZA has not been evaluated in a pediatric population; the product is not indicated for use in children.

The following substantive review issues were raised at the LCM with the applicant, and subsequently addressed during the review:

1) Inadequate information is available related to the bridging of clinical trial formulations to the final to-be-marketed formulation. A June 19, 2013, amendment was under review at the time of the LCM. In this submission, the applicant demonstrated that clinical trial Formulations A and B bridge to the final to-be-marketed CF Formulation.

2) At the LCM, the Division noted that product use would not be recommended in labeling for women with renal or hepatic impairment, or in women > 75 years of age. The basis for these recommendations is as follows:

Renal impairment. The pharmacokinetics of CE/BZA have not been evaluated in women with renal impairment. The **Dosing and Administration** section, **Use in Patients with Renal Impairment** subsection, of the product label will recommend against product use in women with renal impairment.

Hepatic impairment. The pharmacokinetics, safety, and efficacy of CE/BZA have not been evaluated in women with hepatic impairment. No pharmacokinetic studies with CE were conducted in women with hepatic impairment.

In a pharmacokinetic study of BZA 20 mg alone, C_{max} and AUC increased 67% and 143%, respectively, in women with mild hepatic impairment (Child Pugh Class A, N=6), compared to healthy subjects. The C_{max} and AUC of BZA increased 32% and 109%, respectively, in women with moderate hepatic impairment (Child Pugh Class B, N=6). The C_{max} and AUC of BZA increased 20% and 268%, respectively, in women with severe hepatic impairment (Child Pugh Class C, N=6). The half-life of BZA was prolonged from 32 to 50 hours in women with severe hepatic impairment.

The use of CE/BZA in women with hepatic impairment will be contraindicated in product labeling.

Effect of age. The pharmacokinetic profile of CE/BZA has not been evaluated in the elderly. Clinical trials of CE/BZA did not enroll women > 75 years of age.

The pharmacokinetics of a single 20 mg dose of BZA were evaluated in postmenopausal women. Compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC, and women ≥ 75 years of age (n=8) showed a 2.6-fold increase in AUC. This increase in BZA exposure could result in loss of CE efficacy.

The **Dosing and Administration** section, **Use in the Elderly** subsection, of the product label will recommend against product use in women over 75 years.

Retention of Source Documents

Due to natural disaster, clerical errors, or unknown random events, source documentation was partially or completely missing in approximately 8% of subjects in Study 303 (PMO indication), in 1.5% of subjects in Study 305 (VMS indication), and in approximately 8% of subjects in Study 306 (VVA indication).

The following substantive review issue was raised at the LCM with the applicant and addressed during the review as follows:

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Concerns regarding the reliability of data from Study 303 were raised due to the recent (May 23, 2013) submission of adverse event reports from a trial that was completed in 2006. The Division asked why approximately ten percent of the subject files from Site 447 in Brazil appeared to be missing at random.

The applicant explained that Site 447 was inspected in January 2013 and four discrepancies between source files and case report forms were noted, but that none of these recently reported adverse events changed the overall adverse event profile of the product. The applicant attributed the missing subject files to closure of the site and movement of those files between the site and the storage facilities. The applicant stated that they conducted both internal and third-party quality assurance inspections and determined that the pattern of missing subject files was random in nature, but that they were unable to identify the reason(s) for the missing files.

On August 2, 2013, the Office of Scientific Investigations finalized its recommendations regarding the clinical site inspectional findings. The Division was advised to consider the implications of missing records in its assessment of efficacy. Re-analyses of efficacy removing data from participants with missing source documentation were performed; removal of these data did not adversely affect the efficacy findings from either Study 303 (PMO indication) or Study 305 (VMS indication). (b) (4)

Efficacy

Treatment of vasomotor symptoms (VMS). The efficacy of CE 0.45/BZA 20 as a treatment for moderate to severe vasomotor symptoms associated with menopause was established in a 12-week randomized, double-blind, placebo-controlled trial (Study 305). A total of 318 women, ages 42-64 (mean age 53 years) with an intact uterus who had at least 7 moderate to severe hot flushes per day or at least 50 per week at baseline were evaluated. Of these, 127 women were assigned to CE 0.45/BZA 20, (b) (4) women to CE 0.625/BZA 20, and 63 women were assigned to placebo.

Treatment with either CE/BZA dose significantly reduced the number and severity of hot flushes, as measured by the daily severity (b) (4) compared with placebo at Weeks 4 and 12 ($p < 0.001$ for each efficacy measure at each time point). A re-analysis of efficacy endpoints with removal of data from subjects with missing records did not alter the results. There (b) (4)

(b) (4)
CE 0.45/BZA 20 dose is recommended for approval. NDA 022247/Original 2 containing information supporting the use of CE 0.625/BZA 20 for VMS will receive a Complete Response action.

Prevention of postmenopausal osteoporosis (PMO). The efficacy of CE 0.45/BZA 20 for the prevention of postmenopausal osteoporosis was established in two randomized controlled trials that assessed changes in bone mineral density.[2]

Study 303 was a 24-month, double-blind, randomized, placebo- and active-controlled trial evaluating multiple combinations of CE/BZA (including CE 0.45/BZA 20) and placebo on bone mineral density. A total of 3,397 women ages 40-75 (mean age 56 years) with an intact uterus were evaluated.

Prevention of osteoporosis was assessed in two subgroups: 1) 1454 women at least 5 years from their last menstrual period (mean 11 years), and 2) 861 women between 1 and 5 years since menopause (mean 3 years). Women in these subgroups had a mean age of 59 and 52 years, and a mean baseline lumbar spine

[2] In general, for all agents except estrogens, fracture efficacy must be demonstrated prior to accepting changes in bone mineral density as the endpoint for a prevention indication. Based on epidemiologic data, estrogens have been shown to have fracture efficacy. Based on clinical trial data, BZA 20 mg monotherapy has been shown to reduce the risk of fractures.

T- (b) (4) of -1.47 and -0.83, respectively. Women in both groups took calcium (600-1200 mg) and vitamin D (200-400 IU) daily.

Treatment with either CE/BZA dose significantly increased lumbar spine BMD at 24 months compared to placebo in both groups of postmenopausal women ($p< 0.001$). Treatment with either CE/BZA dose also increased total hip bone mineral density in both groups. A re-analysis of efficacy endpoints with removal of data from subjects with missing records did not alter the results. (b) (4)

Study 3307 was a 12-month, double-blind, randomized, placebo- and active-controlled trial; a total of 1,843 women, ages 41-64 (mean age 54 years) were evaluated. Of these, 590 women were less than 5 years postmenopausal (mean 2.5 years). The mean baseline lumber spine T- (b) (4) was -0.91 in women treated with CE 0.45/BZA 20 or CE 0.625/BZA 20, and -0.95 in women in the placebo group. Women took calcium (600 mg) and vitamin D (400 IU) daily.

Treatment with either CE/BZA dose significantly increased mean lumbar spine bone mineral density at 12 months compared to placebo in women who had been postmenopausal between 1 and 5 years (mean 2.5 years). Total hip bone mineral density was also increased with CE/BZA treatment relative to placebo. (b) (4)

Fracture efficacy for CE/BZA was not formally assessed in this development program. Fractures were captured as adverse events; the incidence of fractures was low in both CE/BZA- and placebo-treated women.

Only the CE 0.45/BZA 20 dose is recommended for approval. The **Indications and Usage** section, **Limitation of Use** subsection, will include language that is consistent with the labeling for other conjugated estrogens, namely, that product use only for the prevention of postmenopausal osteoporosis should be limited to women at significant risk of osteoporosis after non-estrogen alternatives have been carefully considered.

(b) (4) NDA 022247/Original 2 containing information supporting the use of CE 0.625/BZA 20 for PMO will receive a Complete Response action.

Treatment of vulvar and vaginal atrophy (VVA). (b) (4)

(b) (4) The applicant is only seeking approval for CE 0.625/BZA 20.

The following substantive review issue was raised at the LCM with the applicant and has been addressed as follows:

(b) (4) NDA 022247/Original 2 containing information supporting the use of CE 0.625/BZA 20 for VVA will receive a Complete Response action.

Safety

The safety of CE/BZA was evaluated in four phase 3 clinical trials ranging from 12 weeks to 24 months in duration and enrolling 6,210 postmenopausal women ages 40 to 75 years (mean age 55 years). Among these, 1,224 women were treated with CE 0.45/BZA 20, and 1,069 women received placebo.

The incidence of all cause mortality, serious adverse events, and neoplasia was low in both CE/BZA and placebo-treated women. The percentage of women who withdrew from treatment due to adverse events was 7.5% and 10% in CE/BZA- and placebo-treated women, respectively. The most common adverse events leading to discontinuation were hot flushes, abdominal pain, and nausea.

Venous and arterial thromboembolism (VTE and ATE). Venous thromboembolism and arterial thombotic events (including stroke and myocardial infarction) are known to occur with administration of both conjugated estrogens and estrogen agonist/antagonists. The incidence of VTE and arterial thrombotic events was low in both CE/BZA- and placebo-treated subjects.

Consistent with the labeling for other products containing CE, use of CE/BZA will be contraindicated in women with an active or a past history of VTE or arterial thrombotic events.

At the LCM, the Division noted that estrogen class labeling would be included in product labeling for CE/BZA. This would include standard wording for the contraindications, boxed warnings, and warnings and precautions sections, as well as descriptions of the results of the Women's Health Initiative estrogen-alone substudies.

Effects on the endometrium. The role of bazedoxifene in the CE/BZA combination is to provide endometrial protection in lieu of a progestational agent. Adequate protection is defined as an endometrial hyperplasia rate after 12 months of $\leq$ 1% (with the upper bound of the one-sided 95% CI $\leq$ 4%).[3]

In Study 303, the probability of endometrial hyperplasia was assessed for combinations of CE 0.45 mg and BZA 10, 20, or 40 mg, and for combinations of CE 0.625 mg and BZA 10, 20, or 40 mg. At month 12, the endometrial hyperplasia rate exceeded 1% for CE 0.625/BZA 10 (at 3.8%); at month 24, the endometrial rate exceeded 1% for CE 0.45/BZA 10 and CE 0.625/BZA 10 (at 2.5% and 7.1%, respectively).

In Study 303, combinations of CE with BZA 20 or 40 mg had acceptable endometrial hyperplasia rates. This finding was replicated in Study 3307 (which used the same formulation); the endometrial hyperplasia rate at month 12 in this trial was less than 1% for both CE 0.45/BZA 20 and CE 0.625/BZA 20.

In Study 304, during the second year, subjects were switched from Formulation B to Formulation C, which contained a BZA component that was less bioavailable than that of Formulation A used in Study 303 and 3307. In Study 304, women with 12 and 24 month exposures to CE 0.425/BZA 20 had acceptable endometrial hyperplasia rates; (b) (4)

The following substantive review issue was raised at the LCM with the applicant and addressed during the review as follows:

(b) (4)

[3] *See* Draft Guidance for Industry: *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations of Clinical Evaluation*, 2003.

Vaginal Bleeding. Vaginal bleeding and spotting are known to occur with use of combination conjugated estrogen/medroxyprogesterone acetate products. Similarly, the combination of CE with an estrogen agonist-antagonist such as BZA may provide incomplete protection from vaginal bleeding and spotting. Vaginal bleeding was reported with similar frequency in subjects on CE 0.45/BZA 20, CE 0.625/BZA 20, and placebo (4-5%).

Fractures. Fractures were reported with similar frequency in subjects on CE 0.45/BZA 20, on CE 0.625/BZA 20, and on placebo (1-2%). The most common types of fractures reported were foot, rib, and wrist fractures.

Pregnancy and Nursing Considerations

CE/BZA will be designated as Pregnancy Category X and must not be used in women who are or may become pregnant.

No studies were performed on animals to evaluate the effects on reproduction with CE/BZA.

Administration of BZA to rats at maternally toxic dosages $\geq$ 1 mg/kg/day ($\geq$ 0.3 times the human AUC at the 20 mg dose) resulted in reduced numbers of live fetuses and/or reductions in fetal body weights. No fetal developmental anomalies were observed. In studies conducted with pregnant rabbits treated with BZA, abortion and an increased incidence of heart (ventricular septal defect) and skeletal system (ossification delays, misshapen or misaligned bones, primarily of the spine and skull) anomalies in the fetuses were present at maternally toxic dosages of $\geq$ 0.5 mg/kg/day (twice the human AUC at the 20 mg dose.

Duavee should not be used by lactating women. It is not known whether the drug is excreted in human milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

Tradename Review

On June 18, 2013, the applicant was notified that the proposed tradename "Duavee" is acceptable.

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The pediatric study requirement for this application will be waived because necessary studies are impossible or highly impracticable as the approved indications apply to conditions that do not occur in the pediatric population.

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of increased concentrations of conjugated estrogens in the presence of a strong CYP3A4 inhibitor. These increased concentrations may increase the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of increased concentrations of conjugated estrogens in the presence of a strong CYP3A4 inhibitor. These increased concentrations may increase the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Therefore, based on appropriate scientific data, FDA has determined that the applicant will be required to conduct a pharmacokinetic trial evaluating the effect of a strong CYP3A4 inhibitor on the exposure of conjugated estrogens and bazedoxifene in obese and non-obese women.

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/s/

JULIE G BEITZ
10/03/2013

FINAL
(September 27, 2013)
Addendum to Original Review Dated June 5, 2013
Clinical Pharmacology Review
Office of Clinical Pharmacology (OCP)

NDA: 022247 Dates of Submission: September 26, 2012 (original submission cover letter)
October 3, 2012 (receipt date of original submission)

Generic Name:	Conjugated Estrogens (CE)/Bazedoxifene (BZA)
Brand Name:	Duavee™
Formulation:	Tablet
Strengths:	CE 0.45 mg/ BZA 20 mg and CE 0.625 mg/BZA 20 mg
Rout of Administration:	Oral
Indications:	• Treatment of moderate to severe vasomotor symptoms (VMS) • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) • Prevention of postmenopausal osteoporosis (PMO)
Dosage and Administration:	For VMS: CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg QD For VVA**:** CE 0.625 mg/BZA 20 mg QD For PMO: CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg QD
Type of Submission:	Original NDA (New Molecular Entity, NME)
Sponsor:	Wyeth/Pfizer
OCP Division:	Division of Clinical Pharmacology-3 (DCP-3)
Office of New Drugs (OND) Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Primary Clinical Pharmacology Reviewers:	Sayed (Sam) Al Habet, R.Ph., Ph.D. LaiMing Lee, Ph.D.
Clinical Pharmacology Team Leader:	Myong-Jin Kim, Pharm.D.
Primary Pharmacometric Reviewer:	Fang Li, Ph.D.
Pharmacometric Team Leader:	Yaning Wang, Ph.D.
Division Director:	E. Dennis Bashaw, Pharm.D.

Reference ID: 3380135

Synopsis:

This is an addendum to the Clinical Pharmacology review dated June 5, 2013. The purpose of this addendum is to describe the background for requesting a Post-Marketing Requirement (PMR) and to summarize the discussion with the sponsor regarding the PMR study.

The objective of the PMR is to evaluate the effect of a strong CYP3A4 inhibitor and body weight on the exposure of conjugated estrogens and bazedoxifene. On September 20, 2013 the sponsor agreed to conduct the PMR study.

It should be noted that only CE 0.45 mg/BZA 20 mg dose will be approved for PMO and VMS indications.

What is the Rationale for the PMR?

In the currently FDA approved Premarin® (conjugated estrogen) label, the following class language is in Drug Interaction Section:

"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."

(b) (4) However, as detailed in the original review dated June 5, 2013 and in the addendum dated June 21, 2013, the ratio of estrogen to BZA is critical for the maintenance of endometrial protection. In other words, the BZA exposure must be adequate to suppress endometrial hyperplasia induced by estrogen. If estrogen exposure increases when co-administered with strong CYP3A4 inhibitors, BZA exposure may be inadequate (see original review dated June 5, 2013 and the addendum dated June 21, 2013).

Furthermore, there is a trend for decrease in BZA exposure in overweight patients with a BMI >27 kg/m^2 (addendum dated June 21, 2013).

These concerns were communicated to the sponsor via an advice letter dated September 12, 2013 as follows:

"*Currently all conjugated estrogen products contain a class warning statement regarding the potential for increased levels of CE in the presence of 3A4 inhibitors. Given the concerns surrounding the ratio of CE to BZA in the dose ranging studies we believe that this would be an appropriate study for a Postmarketing Study Requirement (PMR). In terms of general study*

design, the study should be a multiple dose study and should employ the to-be-marketed dosage form given with a strong 3A4 inhibitor. Additionally, given the concerns noted regarding the effect of body weight in women with a BMI >27, either a second arm in the trial or an additional study that would enroll women of BMI's in the obese range should be included. While neither of these studies would produce any valid risk estimates per se (they are not powered for that consideration), the increase in CE levels and change in CE to BZA ratio would translate to some degree into a safety signal that could be translated into labeling.

To finalize the PMR, we will need to agree on timelines for final protocol submission, study completion, and submission of the complete study report to FDA."

In addition, the PMR was discussed with the sponsor at the teleconference held on September 17, 2013. On September 20, 2013 the sponsor agreed to conduct the PMR study and provided the following synopsis/response:

"Wyeth agrees to conduct a pharmacokinetic study evaluating the ratio of conjugated estrogens to bazedoxifene in the presence of a strong CYP3A4 inhibitor. Wyeth proposes that the design of this study will be a two-period, one-sequence, parallel-group study conducted in postmenopausal women with BMI values <30 (non-obese) or ≥30 (obese).

Wyeth proposes the following title for this study: "A Phase 1, Open-Label, Two-Period, Fixed-Sequence Study to Estimate the Effects of Steady State Administration of a Strong CYP3A4 Inhibitor on the Single-Dose Pharmacokinetics of Conjugated Estrogens/Bazedoxifene in Non-obese (BMI <30) and Obese (BMI ≥30) Postmenopausal Women."

The rationale for selecting the BMI cut-offs of < and >30 mg [kg/m^2] *to define non-obese and obese is based on the World Health Organization definition of obesity.*

Wyeth proposes the following timelines for final protocol submission, study completion, and submission of the complete study report to FDA:

Protocol Submission Date: April 1, 2014
Study Completion Date: December 1, 2014
Final Report Submission: April 1, 2015

Please note that the protocol submission date of April 1, 2014 reflects the date at which the final protocol would be submitted to the NDA. As discussed in the teleconference of September 17, 2013, Wyeth will be seeking the Agency's input into the design of the study and intends to submit

a draft protocol by January 1, 2014. Thus, the Protocol Submission Date reflects the time it may take to reach agreement with FDA on the appropriate design of the study."

Recommendation:

From the Clinical Pharmacology perspective, the sponsor's preliminary/draft proposal is acceptable at this time. The final study protocol will be reviewed when submitted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAYED AL HABET
09/27/2013

LAI M LEE
09/27/2013

MYONG JIN KIM
09/27/2013

EDWARD D BASHAW
09/27/2013
Concur with PMR as outlined in this addendum review. Concur with the deadline of the FINAL protocol to be submitted to the Agency by April 1, 2014.

The Pharmacometics reviewer and Team Lead, Drs. Fang Li and Yanning Wang, respectively, have concurred as well.

Final
(August 20, 2013)
Addendum to Original Review Dated June 5, 2013
Clinical Pharmacology Review
Office of Clinical Pharmacology (OCP)

NDA: 022247 Dates of Submission: September 26, 2012 (original submission cover letter)
October 3, 2012 (receipt date of original submission)
June 19, 2013 (response to IR letter)

Generic Name:	Bazedoxifene (BZA)/Conjugated Estrogens (CE)
Brand Name:	Duavee™
Formulation:	Tablet
Strengths:	20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE
Rout of Administration:	Oral
Indications:	• Treatment of moderate to severe vasomotor symptoms (VMS) • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) • Prevention of postmenopausal osteoporosis (PMO)
Dosage and Administration:	For VMS: BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg QD For VVA**:** BZA 20 mg/CE 0.625 mg QD For PMO: BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg QD
Type of Submission:	Original NDA (New Molecular Entity, NME)
Sponsor:	Wyeth/Pfizer
OCP Division:	Division of Clinical Pharmacology 3
Office of New Drugs (OND) Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Primary Clinical Pharmacology Reviewers:	Sayed (Sam) Al Habet, R.Ph., Ph.D. LaiMing Lee, Ph.D.
Clinical Pharmacology Team Leader:	Myong-Jin Kim, Pharm.D.
Primary Pharmacometric Reviewer:	Fang Li, Ph.D.
Pharmacometric Team Leader (Acting):	Jeffry Florian, Ph.D. (signing for Yaning Wang, Ph.D.)
Division Director:	E. Dennis Bashaw, Pharm.D.

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Recommendation:

The NDA is acceptable from the clinical pharmacology perspective. This addendum supersedes the original review dated June 5, 2013 in reference to the acceptability of the NDA pending clarification of formulation bridging.

Based on the submitted data and justifications that was provided by the sponsor on June 19, 2013, it can be concluded that Formulations A and B used in the pivotal Phase III studies in this NDA are bioequivalent to the proposed commercial formulation (CF). No further action is indicated at this time regarding this issue.

Executive Summary:

This addendum is to the clinical pharmacology review dated June 5, 2013. The primary purpose of this addendum is to address bridging of the clinical trial formulations to the to-be-marketed (TBM) formulations and to provide clarification/correction to some of the information related to bridging in the original review. The secondary purposes of this addendum are to provide detail information on the bio- analytical methods and an analysis of the effect of body weight on the safety and efficacy of BZA/CE.

In the original NDA, there were four major formulations, A, B, C, and D. Formulation "D" was originally identified by the sponsor as the potential TBM formulation. However, it was later found that Formulation "D" was not bioequivalent to the original Formulation A used in pivotal clinical Phase III studies. Due to the lack of adequate bridging between the potential TBM Formulation "D" and "A", the sponsor developed a series of potential TBM/test formulations (e.g., E, F, G, and 1, 2, 3). Based on a series of bioequivalence (BE) studies, only Formulation "F" was found bioequivalent to Formulation "A" and this was designated as the final TBM Formulation (also called Commercial Formulation or CF). (See also original Clinical Pharmacology review dated June 5, 2013 for further details).

In addition, Formulation "C" used in only one Phase III trial (Study # 304) was found **not** to be bioequivalent to the original formulation "A" in four BEstudies. Therefore, the sponsor conducted new study (Study #3307) using the Formulation "A" as a replacement to Study # 304. Based on this, Formulation "C" becomes irrelevant from the bridging perspective. However, the data obtained from Study # 304 were considered supportive that provided some important safety information related to decrease in endometrial protection associated with low exposure to BZA from Formulation "C" (See also original Clinical Pharmacology review dated June 5, 2013 for further details).

Therefore, the focus of this addendum is to ensure that there is adequate bridging between Formulations "A" and "B" with the TBM formulation (CF). The reason for focusing on formulation "A" and "B" is because they were used in the pivotal Phase III studies to support the approval.

It should be noted that the bridging is primarily related to BZA component of the product for three primary reasons: 1) In most of the BE studies all CE components passed the BE criteria

with a couple of exception (see original review), 2) In four BE studies (114, 1117, 1120, 112), Formulation C failed to meet BE criteria due to BZA component and not due to CE component, and 3) BZA exposure was found to be critical to provide adequate endometrial protection (see original OCP and the Medical Officers' reviews). Therefore, all the discussion is pertain to BZA component (see later discussion and list of CE components).

Overall Conclusions:

- Based on our analysis and interpretation of all supporting documents that were submitted by the sponsor on June 19, 2013 and the discussion at the mid cycle meeting held with the sponsor on June 26, 2013, we concluded that Formulations "A" and "B" are bioequivalent to the final TBM formulation, which is the new Formulation "F" (see also meeting minutes dated July 25, 2013).
- The bioanalytical methodologies were found adequate.
- There were no issues involving quality assurance in reference to the analytical laboratories, (b) (4) for BZA (see OCP review dated February 21, 2008 (b) (4)).
- Additional analysis of the PK data shows that body weight may play an important role on the BZA exposure. From this analysis, BZA clearance appears to increase with body weight (i.e., lower exposure with increase body weight).
- (b) (4)

Summary of Formulation Bridging Issues:

In the original submission the bridging processes were not clear due to many issues including but not limited to confusion in stock numbers, batch numbers, identity of the formulations, and the changes made throughout the 10 years of formulation development.

Due to the complexity of the biopharmaceutics and formulation program, an information request (IR) letter was sent to the sponsor on March 21, 2013 to provide clarification on bridging of all the formulations. On April 5, 2013, the sponsor provided a response including several figures and tables.

However, further review of the available information in the original NDA and the response to the IR letter dated March 21, 2013, it was noted that there were still many inconsistencies, inaccuracies, and confusion in reference to stock number, batch numbers, and formulations used in various studies. Based on that, a second IR letter was sent to the sponsor on May 24, 2013.

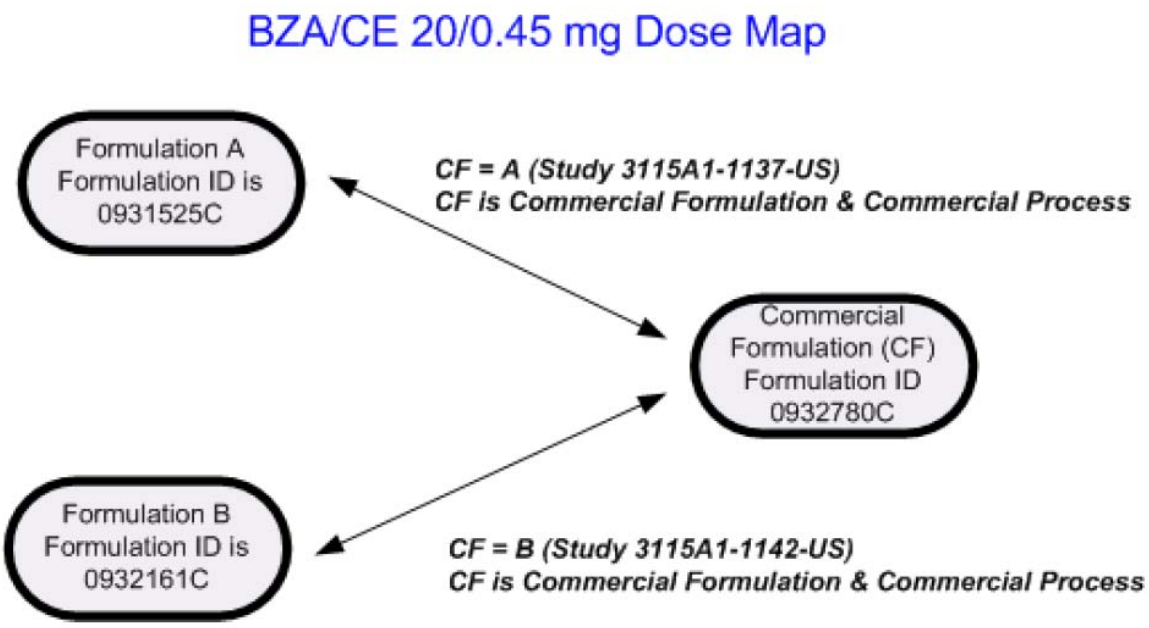
On June 19, 2013 the sponsor responded to the second IR letter and included updated figures, several detailed tables, revised summary Sections of the Summary of the Biopharmaceutics Studies (Section 2.7), Pharmaceutical Development (Section 3.2.P.2), batch analysis, and several Appendices.

Reviewer's Comments and Analysis of Formulations Bridging:

Figures 1 and 2 show the bridging between Formulations A and B used in pivotal Phase III studies to the commercial formulations (CF) for both tablet BZA/CE strengths (20/0.45 mg and 20/0.625 mg). The studies supporting this bridging are included in these Figures.

Figure 1. Bridging 20/0.625 mg Strength

Figure 2. Bridging 20/0.45 mg Strength



The above figures are based on the following pivotal BE studies:

- Study 1122: Formulation A vs proposed TBM formulation for BZA 20 mg/CE 0.625 mg dose strength
- Study 1137: Formulation A vs proposed TBM formulation for BZA 20 mg/CE 0.45 mg dose strength
- Study 1139: Formulation B vs proposed TBM formulation for BZA 20 mg/CE 0.625 mg dose strength
- Study 1142: Formulation B vs proposed TBM formulation for BZA 20 mg/CE 0.45 mg dose strength

In addition, study 1117 shows bridging between Formulations A and B for BZA 20 mg/CE 0.625 mg dose strength.

Figures 3-5 show detailed linkage among all relevant formulations used in this NDA, sequence of product changes, including a roadmap for decisions that led from the first formulation to the final commercial formulation as well as an explanation of the specific manufacturing differences (e.g., processes, (b) (4) procedures, manufacturing sites).

As shown in these Figures, while several BE studies were performed over the course of 10 years development, four studies are considered pivotal to demonstrate the BE between the Phase III formulations and commercial formulations (CF). These studies are 1122, 1137, 1139, and 1142 which are cited in **Figures 1 to 5**.

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Formulation Terminology:

In the response to the second IR letter, the sponsor compared and clarified the formulation terminology used across the product development history in a tabulated format and consistently adhered to the terminology throughout the response document.

A comprehensive tabular summary of each BE study related to development decisions for each BZA/CE dose strength was provided by the sponsor to identify each formulation. Furthermore, the sponsor provided response to the FDA's specific question to clarify the "TBM" formulation in Study 1117 and its relation with the final TBM formulations in Studies 1122 and 1137. The response provided was found to be helpful and adequate.

Impact of Manufacturing Sites:

One issue that is worth mentioning in this addendum is the impact of the manufacturing site in reference to scale-up on the *in vivo* performance of the formulations. The sponsor used two primary manufacturing sites, one in Montreal and the other in (b) (4) In the (b) (4) facility two different manufacturing processes were employed for the clinical supplies (see ONDQA/CMC reviews).

(b) (4)

Clarification of Commercial Formulation (CF)

As stated earlier, one of the issues is the lack of consistent terminology used throughout the original submission which created confusion and in particular related the TBM formulations used in various BE studies. In this submission, the sponsor provided adequately clarification to our question.

Based on the sponsor's response, it becomes clear that the "CF" formulation is the final TBM (b) (4)

In addition the sponsor provided clarification about the manufacturing process for specific batches. (b) (4)

(b) (4)

Clarification of CF Formulations Used in BE Studies 1122 and 1137:

The sponsor provided adequate clarification to the FDA's specific question related to the CF formulations used in the BE studies 1122 and 1137. Based on the response it was clear that the batch used in Study 1117 was not manufactured in accordance with the proposed CP process and was designated as Commercial Formulation (First Manufacture, or **CF-FM**). However, the CF formulation in Study 1122 was manufactured in accordance with the proposed CP process (**CF-CP**). The sponsor also clarified that there was no direct relationship between CF Formulation used in Studies 1137 and 1117.

Reviewer's General Comments on Exposure-response and Product Quality:

From the clinical pharmacology perspective, as shown above and was discussed in details in the original clinical pharmacology review dated June 5, 2013 as well as the ONDQA/CMC reviews, the robustness of the product quality and assurance is essentially critical for the following reasons:

Exposure-Response:

- (b) (4) (b) (4). In the original review it was noted that lowering BZA exposure by small percentage was associated with decrease in endometrial protection (see original NDA review).
- This product will be administered chronically to relatively healthy subjects to improve bothersome conditions, VMS and VVA, to improve the life style of the subjects. However, osteoporosis is an exception which is associated with bone loses. Therefore, the risk/benefit ratio should be carefully assessed (see below).
- BZA is associated with relatively serious safety risks such as venous thrombotic events (VTE) (b) (4)
- CE on the other hand is also known to be associated with other risks upon chronic administration such as endometrial hyperplasia. The main rationale for the use of BZA is to provide protective effect to endometrium associated with CE.
- The extensive analysis of the data in the original clinical pharmacology review and the Medical Officer's review reveals that small changes in BZA exposure has been associated with decrease in protective effect to endometrial. (b) (4)

Product Quality:

(b) (4)

(b) (4)

Based on the above, it appears that any minor changes (b) (4) have significant effect on the *in vivo* performance of the final product. This is in addition to other intrinsic and extrinsic factors that were addressed in the original review.

To conclude, this issue does not rest solely with the Clinical Pharmacology team, but it is considered multi-discipline including clinical and in particular ONDQA/CMC team.

Overall Conclusion in Reference to Bridging:

Based on the submitted data and justifications it can be concluded that Formulations A and B are bioequivalent to the new commercial formulation (CF) formerly known as Formulation "F".

Bioanalytical:

For BZA the method used in the monotherapy program is the same as that used in the combination therapy program. Similarly, the LC/MS/MS assays for CE measurement used in this NDA is also well established the same sponsor (Wyeth/Pfizer) for Premarin® (see below).

BZA:

As stated earlier, the focus of this addendum and the review is on BZA assessment in terms of *in vitro* and *in vivo* performance, systemic exposure, and bioequivalence from different formations. Therefore, it is critical that the analytical methodologies must be robust to accurately measure BZA concentrations in the plasma.

The analytical method for the determination of the plasma BZA and its metabolites was already reviewed and accepted by the Office of Clinical Pharmacology (b) (4)

Briefly, this was a high performance liquid chromatography (HPLC)-fluorescence and liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation was 25 pg/mL.

It should be noted that several HPLC methods with fluorescence detection were initially developed and validated for the quantitation of BZA in plasma. The method employed for many monotherapy BZA studies utilized [redacted] (b) (4)

HPLC/fluorescence methods were also developed for the quantitation of total (conjugated and unconjugated) BZA in plasma. Liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods for the quantitation of BZA in plasma were also developed and used later in the BZA/CE development program. The LLOQ for all these methods ranged from20 pg/mL to 250 pg/mL, depending on the plasma volume used which ranges from 0.2 mL to 1 mL. **Table 8** shows a summary of the precision of the analytical method per the sample volume and concentration. It should be noted that **Table 8** was submitted in the current NDA. In addition, it was submitted, referenced and reviewed by OCP for monotherapy program (see OCP review dated March 21, 2007).

Table 8. Specification of BZA Bioanalytical Methods (Source: Submissions dated September 26, 2012 and June 19, 2013, Section 2.7.1, Table 3-4 and OCP review Dated March 21, 2007, Table 27, Page 29).

Report	Analytical Method	Matrix	Sample Volume	LLOQ	Linear Range	Analytical Site
---------- Bazedoxifene (Unconjugated) ----------						
GTR-33183	HPLC/with fluorescence	Plasma	1 mL	25 pg/mL	25-2500 pg/mL	Wyeth Research
GTR-36853	HPLC/with fluorescence	Plasma	1 mL	25 pg/mL	25-2500 pg/mL	Wyeth Research
GTR-33785	HPLC/with fluorescence	Plasma	1 mL	20 pg/mL	20-2000 pg/mL	(b) (4)
GTR-38036	HPLC/with fluorescence	Plasma	1 mL	25 pg/mL	25-2500 pg/mL	
RPT-42781	LC/MS/MS	Plasma	1 mL	25 pg/mL	25-2500 pg/mL	
RPT-44980	LC/MS/MS	Plasma	0.5 mL	40 pg/mL	40-10,000 pg/mL	
RPT-50218	LC/MS/MS	Plasma	0.5 mL	20 pg/mL	20-10,000 pg/mL	
RPT-48099	HPLC/with fluorescence	Ultrafiltrate	0.2 mL	0.5 ng/mL	0.5-25 ng/mL	Wyeth Research
---------- Total Bazedoxifene (Unconjugated and Conjugated) ----------						
GTR-33183	HPLC/with fluorescence	Plasma	0.2 mL	125 pg/mL	125-12,500 pg/mL	Wyeth Research
GTR-36407	HPLC/with fluorescence	Plasma	0.2 mL	250 pg/mL	250-12,500 pg/mL	Wyeth Research
GTR-36595	HPLC/with fluorescence	Plasma	0.2 mL	250 pg/mL	250-12,500 pg/mL	(b) (4)

(b) (4) GTR = general technical report; RPT = report, HPLC = high-performance liquid chromatography; LC/MS/MS = liquid chromatography/tandem mass spectrometry; LLOQ = lower limit of quantitation; (b) (4)

The calibration curve was linear over 40 to 10,000 pg/mL with a regression line (r) of 0.9977. Individual data were examined for consistency and accuracy throughout this NDA. The data was acceptable from the analytical assay perspective.

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Conjugated Estrogens (CE):

The following components were analyzed and reported in this NDA in almost all BE/BA studies as shown in **Table 9** from a typical BE study:

Table 9. CE Components Commonly Determined in BE Studies in this NDA

Analyte	Comparison[a]	
	C_{max}	AUC
Unconjugated Estrone	96 - 106	96 - 107
Unconjugated Estrone Adjusted for Baseline	90 - 107	89 - 108
Unconjugated Equilin	91 - 104	-
Unconjugated 17β-estradiol	93 - 106	85 – 102
Unconjugated 17β-estradiol Adjusted for Baseline	86 - 103	94 - 111
Unconjugated 17β-dihydroequilin	95 - 111	102 - 120
Unconjugated $\Delta^{8,9}$-dehydroestrone	-	-
Unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol	88 - 101	-
Total Estrone	98 - 110	95 – 104
Total Estrone Adjusted for Baseline	96 - 109	91 - 103
Total Equilin	101 - 118	100 - 112
Total 17β-estradiol	99 - 117	95 – 107
Total 17β-estradiol Adjusted for Baseline	99 - 119	93 – 106
Total 17β-dihydroequilin	97 - 115	96 – 109
Total $\Delta^{8,9}$-dehydroestrone	102 - 119	103 – 115
Total 17β-$\Delta^{8,9}$-dehydroestradiol	98 - 111	97 – 110
Bazedoxifene	86 - 112	92 -110

a. Formulation F (Test) vs. Formulation A (Reference)

The intraday precision and accuracy were < 15% for the HPLC-fluorescence assays. The interday precision and accuracy (determined via the low, mid, and high quality control (QC) samples) were < 15% coefficients of variation for the HPLC-fluorescence assays. The intraday and interday precision and accuracy were ± 15% for the mid and high QC samples and ± 20% for the low QC samples for the LC/MS/MS assays (**Tables 10-12**).

In this NDA the sponsor used two main methods for the determination of CE components as follows:

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GC/MS/MS [redacted]):

This method was used for the determination of unconjugated estrone, equilin, Δ8,9-dehydroestrone, 17β-estradiol, 17β-dihydroequilin, and 17β-Δ8,9-dehydroestradiol.

The LLOQ of this method was 2.5 pg/mL for 17β-estradiol; 5.0 pg/mL for estrone, 17β-dihydroequilin, 17β-Δ8,9-dehydroestradiol, and Δ8,9-dehydroestrone; and 10 pg/mL for equilin.

GC/MS/MS (Enzymatic Hydrolysis)

Using both enzymatic hydrolysis and [redacted] the total (unconjugated and conjugated) estrone, equilin, Δ8,9-dehydroestrone, 17β-estradiol, 17β-dihydroequilin, and 17β-Δ8,9-dehydroestradiol concentrations in plasma were determined.

The LLOQ of this method was 50 pg/mL for total equilin; 25 pg/mL for total estrone, Δ8,9-dehydroestrone, 17β-dihydroequilin, and 17β-Δ8,9-dehydroestradiol; and 12.5 pg/mL for total 17β-estradiol.

Since CE (Premarin) has been used for decades, these methods for the determination of CE are well established and validated at many laboratories and in the literature. The following is a summary of the validation for selected components:

Table 10. Intra-Day Precision of Free CE Components (Source Report # RPT-43948)

VALIDATION QCs Intraday Data Analyte (Free)	Maximum Mean Bias (Maximum Mean Intraday Deviation from Nominal)	Maximum Intraday CVs
17ß-Estradiol	-9.80%	12.3%
17ß-Dihydroequilin	-8.00%	11.7%
17ß-$\Delta^{8,9}$ Dehydroestradiol	-6.93%	12.4%
Estrone	-8.90%	12.5%
Equilin	+6.40%	12.5%
$\Delta^{8,9}$ Dehydroestrone	+16.0% (all data) +14.7% (outlier excluded)	27.2% (all data) 10.7% (outlier excluded)

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Table 11. Inter-day Precession of Free CE Components (Source Report # RPT-43948)

VALIDATION QCs Interday Data Analyte (Free)	Maximum Mean Bias (Maximum Mean Interday Deviation from Nominal)	Maximum Interday CVs
17ß-Estradiol	-4.60%	10.2%
17ß-Dihydroequilin	-7.33%	6.71%
17ß-$\Delta^{8,9}$ Dehydroestradiol	-5.33%	6.97%
Estrone	-3.30%	8.59%
Equilin	4.00%	7.88%
$\Delta^{8,9}$ Dehydroestrone	+8.67% (all data) +4.00% (outlier excluded)	19.1% (all data) 11.9% (outlier excluded)

Table 12. Intra-day Precession of Total CE Components (Source Report # RPT-45128)

VALIDATION QCs Intraday Data Analyte (Total)	Maximum Mean Bias (Maximum Mean Intraday Deviation from Nominal)	Maximum Intraday CVs
17ß-Estradiol	-7.90%	4.74%
Repeat Experiment	-8.00%	8.35%
17ß-Dihydroequilin	+4.27%	4.09%
Repeat Experiment	7.73%	6.85%
17ß-$\Delta^{8,9}$Dehydroestradiol	-6.20%	3.65%
Repeat Experiment	-7.70%	3.20%
Estrone	-19.5%	3.31%
Repeat Experiment	-7.87%	7.25%
Equilin	-14.4%	3.56%
Repeat Experiment	-5.00%	4.85
$\Delta^{8,9}$Dehydroestrone	-9.10%	5.65%
Repeat Experiment	10.7%	4.52%

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Reviewer's Comments on Bioanalytical:

The sponsor used adequate and well established methods for the determination of CE components in the plasma. The BZA analytical method is adequate and was used in (b) (4) monotherapy programs (b) (4) and in this NDA. The BZA method was also reviewed by OCP for the monotherapy programs and was found acceptable. Overall, the methods for BZA and CE determination are accurate, sensitive, specific, and reproducible.

Analytical Quality Assurance and Audits:

In the 74-Day letter dated December 12, 2012, the following requests were made by the clinical pharmacology team:

1. Per the February 12, 2008, meeting minutes, resubmit the audit report (b) (4) for the BZA/Atorvastatin drug interaction study (study # 3068A1-126-EU).
2. Provide confirmation that study # 3068A1-126-EU is the only study that was conducted (b) (4)
3. Please provide the list of studies and corresponding audits (if any) that were conducted or analyzed (b) (4)

Response to Requests 1 and 2:

On December 21, 2012 the sponsor responded to the above two requests and re-submitted the audit reports. These audit reports were previously submitted (b) (4) They were reviewed and were found to be acceptable by OCP (see review dated February 21, 2008).

In addition, the sponsor confirmed that Study 3068A1-126-EU was the only study that was conducted (b) (4)

Response to Request 3:

On December 21, 2012, the sponsor responded to third request and resubmitted to the NDA 022247 the correspondence dated October 5, 2011 and January 20, 2012 (b) (4) The only study (b) (4) during the specified period was for measurement of moxifloxacin plasma concentrations for Study # 3068A1-131-US entitled "effects of BZA on cardiac repolarization".

BZA was not impacted (b) (4)

Effect of body weight on BZA exposure and its clinical implication

In addition to formulation, other factors could lower BZA exposure after administration of BZA/CE tablets. One such factor is body weight. The population PK analysis of dense PK data indicated that BZA clearance increased with body weight. Subjects over 75 kg, the average weight of subjects in the dense PK dataset, were observed to have an average clearance that was 17% higher than those with lower body weight (less than or equal to 75 kg). Accordingly, a 17% decrease in BZA exposure is expected in this group of patients. This level of decrease is comparable to that observed in study 304 where an 18-36% decrease in BZA exposure in formulation C showed a significant decrease in endometrial protection. Therefore, overweight, defined as BMI between 25 and 30, was speculated to have a higher rate of hyperplasia because of lower BZA exposure.

Figure 6: Effect of body weight on BZA clearance after administration of BZA/CE tablets

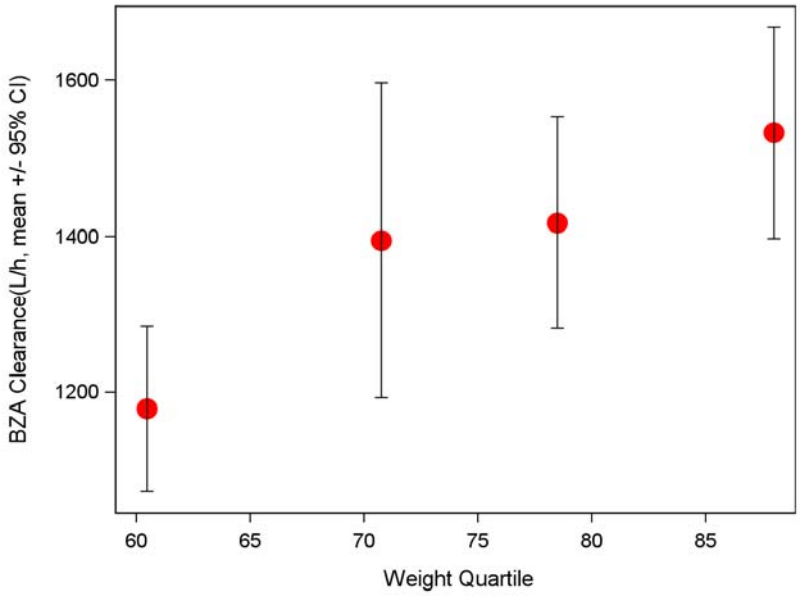

Table 13: BZA clearance by body weight group in dense PK studies

	N	Mean Clearance (L/h)	Std
Body weight < =75 kg*	125	1278	613
Body weight >75 kg	112	1496	524

*Body weight of 75 kg was used as a cut-off because the average weight in the population PK dense dataset was 75 kg.

Further analysis of Phase III data revealed that subjects with BMI >27, the average BMI of the dense PK dataset, were more likely to develop hyperplasia than those with smaller BMI values. In study 303, after 24 months of treatment, there was an imbalance in number of positive hyperplasia cases in overweight patients with CE 0.625 mg. Higher hyperplasia incidence was associated with larger body size. As indicated in **Table 14**, patients with BMI >27 was only 35%

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(n=783 out of 2210) of all patients participated in study 303, but accounted for more than 64% of all positive hyperplasia cases (n=21 out of 33). The effect of BMI on incidence of hyperplasia was significant (chi-square, p< 0.001).

Table 14: Incidence of hyperplasia in study 303 after 24 Months

Study 303 24 Months		**BMI<=27**			**BMI>27**		
		Total	**n**	**%**	**Total**	**n**	**%**
CE 0.45 mg	BZA 10 mg	242	3	1.24	124	5	4.03
	BZA 20 mg	228	2	0.88	145	0	0
	BZA 40 mg	241	0	0	116	0	0
CE 0.625 mg	BZA 10 mg	244	7	2.87	136	14	10.29
	BZA 20 mg	233	0	0	135	2	1.48
	BZA 40 mg	235	0	0	127	0	0
Total		1423	12	0.84	783	21	2.7

Conclusion:

Any factors that could lower BZA exposure will significantly increase the risk of hyperplasia. Here two risk factors were identified: formulation changes and body weight, with both pointing to lower BZA exposure.

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/s/

SAYED AL HABET
08/20/2013

LAI M LEE
08/20/2013

FANG LI
08/20/2013

JEFFRY FLORIAN
08/20/2013

MYONG JIN KIM
08/20/2013

EDWARD D BASHAW
08/21/2013

As the Dir. of the Division of Clinical Pharmacology-3, I am exercising my option to provide clarifying comments on the addendum review:

1.) On pages 4 and 11, bazedoxifene is referred to as having the properties of or being either a "narrow therapeutic range or index" drug. At the current time the FDA does not have a regulatory definition of either. The observation here is inteneded not as a recommendation from the Office of Clinical Pharmacology for a REMS or other regulatory action, merely to highlight the potential for loss of endrometrial protective effects due to minor changes in bazedoxifene levels. The use of the terms here are reflective of their use in the general clin pharm/medical litierature and not as a statement of regulatory finding.

2) Although not contained in either the "Recommendations" section nor the "Executive Summary", the analysis of the pk data across studies shows that increased body weight is associated with an increased clearance of bazedoxifene. Given our concern over the potential for loss of endometrial protection due to lower bazedoxifene levels cited above, this issue should have been highlighted in both areas (see pages 18 and 19 of review).

These are the two substantive issues that I feel needed additional clarification and perspective. I do concur with the finding that Formulation "F" has demonstrated bioequivalence to the clinically studied material.

BIOPHARMACEUTICS REVIEW ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 22-247	**Reviewers:** John Z. Duan, Ph.D.	
Submission Dates:	7/31/2013		
Division:	DRUP	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Wyeth	**Biopharmaceutics Supervisor (acting):** Richard Lostritto, Ph.D.	
Trade Name:	(b) (4)	**Date Assigned:**	11/2/2012
Generic Name:	Bazedoxifene/ Conjugated Estrogens	**Date of Review:**	8/5/2013
Indication:	Treatment of moderate to severe vasomotor symptoms due to menopause; treatment of moderate to severe vulvar and vaginal atrophy; prevention of post-menopausal osteoporosis.	**Type of Submission:** 505(b)(1) Original NDA	
Formulation/Strengths:	Tablet; BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(1) New Drug Application for Bazedoxifene/Conjugated Estrogens (BZA/CE) tablets. The proposed to be marketed tablet strengths are 20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE. The proposed indications are for the treatment of moderate to severe vasomotor symptoms, treatment of moderate to severe vulvar and vaginal atrophy, and prevention of postmenopausal osteoporosis. Bazedoxifene/Conjugated Estrogens (BZA/CE) tablets are a fixed dose combination product (b) (4)

The NDA submission includes an *in vitro in vivo* correlation (IVIVC) (b) (4) of the BZA/CE tablets. During the late cycle communications, the following comments were conveyed to the Applicant.

Although not an approvability issue for this NDA submission, your proposed IVIVC is not acceptable at this time due to the following reasons.

(b) (4)

In addition, the following concerns should be noted:

(b) (4)

Reference ID: 3353453

(b) (4)

(b) (4)

This information is valuable and can be used for further development of this product. If you want to pursue further the IVIVC model, conduct the following:

a. Build an IVIVC model using the bazedoxifene acetate/conjugated estrogens tablet data and validate the model.
b. Show the robustness of the model.

In this submission dated 7/31/2013, the Applicant provides the following response.

Wyeth acknowledges and appreciates the Agency's feedback on the proposed IVIVC model (b) (4) *of the CE/BZA drug product. At this time, Wyeth does not intend to utilize the proposed IVIVC model. However, if Wyeth chooses to pursue the IVIVC model, we will submit the additional information to the Agency to address their recommendations provided above in a future post approval supplement.*

RECOMMENDATION:

The Applicant's response is acceptable. No further action is necessary.

John Duan, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN Z DUAN
08/06/2013

TAPASH K GHOSH
08/07/2013

Final
(June 5, 2013)
Clinical Pharmacology Review
Office of Clinical Pharmacology (OCP)

NDA: 022247 Date of Submission:	September 26, 2012 (cover letter) October 3, 2012 (Receipt date)
Generic Name:	Bazedoxifene (BZA)/Conjugated Estrogens (CE, Premarin®)
Proposed Brand Name:	TBD
Formulation:	Tablet
Strengths:	20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE
Route of Administration:	Oral
Indications:	• Treatment of moderate to severe Vasomotor Symptoms (VMS) • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) • Prevention of postmenopausal osteoporosis (PMO)
Dosage and Administration:	For VMS: BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg QD For VVA**:** BZA 20 mg/CE 0.625 QD For PMO: BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg QD
Type of Submission:	Original NDA (New Molecular Entity, NME)
Sponsor:	Wyeth/Pfizer
OCP Division:	Division of Clinical Pharmacology 3
Office of New Drugs (OND) Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Primary Clinical Pharmacology Reviewers:	Sayed (Sam) Al Habet, RPh, PhD LaiMing Lee, PhD
Clinical Pharmacology Team Leader:	Myong-Jin Kim, Pharm.D.
Primary Pharmacometric Reviewer:	Fang Li, Ph.D.
Pharmacometric Team Leader:	Yaning Wang, Ph.D.
Division Director:	E. Dennis Bashaw, Pharm.D.

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is **not** acceptable at this time due to inadequate information currently available related to bridging all formulations to the final to-be-marketed (TBM) formulation.

An Information Request (IR) letter was sent to the sponsor on May 24, 2013 asking the sponsor to provide clear pathway to the complicated formulation development and bridging all formulations to the TBM formulation. The response is expected to be submitted on/or before June 10, 2013. After reviewing the sponsor's response we will write addendum to this review.

(b) (4) (b) (4)

(b) (4) However, the final assessment of the clinical data is referred to the Medical Officer and the bio-statistical analysis.

1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no post-marketing commitments are indicated for this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

This is a combination of a New Molecular Entity (NME), Bazedoxifene (BZA also known as TSE-424) which is a third generation selective estrogen receptor modulator (SERM) and estrogen receptor agonist, conjugated estrogens (Premarin®). (b) (4) Mechanistically, the combination product is referred to as tissue-selective estrogen complex (TSEC).

(b) (4)

BZA and CE function by binding to and activating the two estrogen receptors (α and β). CE is composed of multiple estrogens that demonstrate tissue selective estrogen receptor agonist

activity. BZA demonstrates both tissue selective estrogen receptor agonist and antagonist activity, exhibiting agonist activity on the skeletal system, while acting as an estrogen antagonist in breast and uterine tissue.

The rationale for the development of BZA/CE is based on the hypothesis that BZA will be acting primarily as an estrogen receptor antagonist in uterine and breast tissue. This will inhibit the proliferative effects of CE on the endometrium and reduce the incidence of uterine bleeding, breast pain/tenderness, and increased breast density associated with existing traditional progestin-containing hormone therapy (HT). CE is expected to effectively relieve menopause related symptoms (e.g., hot flushes, symptoms of VVA, vaginal dryness, and dyspareunia). In addition, in view of the positive effects of CE and BZA on the skeleton, it is expected that the combination of the 2 agents would be effective in the prevention of PMO.

Basic Clinical Pharmacology Information:

Overview:

The sponsor conducted extensive program (b) (4) for this combination product (For details, see the biopharmaceutics Section **2.5** and individual study review Section **4.2**). Many of the studies did not pass the bioequivalence criteria for BZA and/or CE components of the product at either Cmax or AUC levels.

The drug will be administered without regard of food. However, food appears to have modest effect on BZA PK. The dosage and indications are as follows:

- Moderate to severe vasomotor symptoms: 20/0.45 or 20/0.625 mg QD
- Moderate to severe vaginal atrophy: 20/0.625 mg QD
- Prevention of osteoporosis: 20/0.45 or 20/0.625 mg QD

The focus of the findings is on BZA components in this review. Based on the monotherapy and BZA/CE programs the following is a summary of the basic clinical pharmacology findings:

- BZA half-life is approximately 30 h.
- BZA Tmax occurs approximately by 2 hour.
- BZA absolute BA (F) is approximately 6%.
- There is modest effect of food on both BZA and CE components.
- BZA PK is dose-proportional over a range of 2.5 mg to 120 mg.
- BZA steady state levels is about 2 times those after a single dose.
- BZA is highly bound to plasma proteins, approximately 97%. It should be noted that BZA does not affect warfarin, diazepam, or digoxin's plasma protein binding. Also, warfarin, diazepam, or digoxin does not affect BZA plasma protein binding.
- BZA is extensively metabolized primarily by glucuronidation pathways (primarily to active metabolites). It is mainly excreted in bile and feces (>90% of radioactivity recovered in feces). There is some evidence of entero-hepatic circulation due to the second peak (this phenomenon appears to be similar to that observed with raloxifene, Evista™, a pharmacologically similar approved class of drug, NDA 020815).

- 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-Pugh C) compared to healthy subjects. Not recommended in patients with hepatic impairment.
- Not recommended in patients with renal impairment due to lack of adequate information. However, in a small study there was 69% increase in BZA AUC in patients with severe renal impairment (limited comparative data to 2 healthy control subjects).
- It appears that there is an age related increase in BZA exposure. Due to the lack of information from the Phase 3 studies and the 2.6-fold increase in BZA exposure in the elderly women compared to the younger women from monotherapy program ((b) (4) Study 121-US), use of BZA/CE in elderly women (>75 yrs) is not recommended.
- There is no evidence of QTc prolongation at BZA doses of as high as 120 mg.
- Race/Ethnicity does not appear to affect BZA PK.
- There were no major drug-drug interactions with BZA and ibuprofen, atorvastatin, azithromycin, and antacids.

Clinical Program:

The clinical program consists of 5 Phase III studies (303, 304, 305, 306, and 3307) and Phase II study 203. From these studies the following conclusions can be made:

- It appears that the therapeutic window of BZA is narrow. For example, based on Phase II dose finding study (Study 203) any small changes in dose may results in lack of endometrial protection. The study was conducted over 5 to 20 mg doses. Doses of 5 mg and 10 mg of BZA administered with 0.3 mg and 0.625 mg of CE were not deemed to provide adequate endometrial protection. Similarly, BZA 20 mg/0.3 mg CE was **not effective** for the reduction in the severity of hot flushes. (b) (4) . Furthermore, based on three bioequivalent studies, there was approximately 16%-36% reduction in Cmax and AUC of BZA in Study 304 when Formulation B was switched with Formulation C during the study resulted in reduction in endometrial protection (see Biopharmaceutics Section 2.5). Therefore, any factors affecting the systemic exposure of BZA plays critical role in the therapeutic optimization.

- Based on study 303 which used Formation A, it appears that tolerance may be developed with this product for estrogenic efficacies as well as the effect on bone mineral density (BMD). In this study, the highest effect was observed at 12 months of treatment which then narrowed down at 24 months. Therefore, it is not known at this time what would be the efficacy beyond 24 months. In addition, there was little separation between the doses at 24 months. Overall, the effect of the drug is significant compared to placebo for BMD.

- Based on the results from study 303, it can be concluded that both BZA 20 mg/CE 0.625 and BZA 20 mg/CE 0.45 mg were effective in endometrial protection. Both dosing regimen were effective in the prevention of menopausal osteoporosis for up to 24 months.

- Study 3307 was a confirmatory study and a replacement for Study 304 in which one of the formulation (Formulation C) was found to be <u>not</u> equivalent to Formulation A (b) (4) Based on the results from this study it can be concluded that the BZA 20 mg/CE 0.625 mg and BZA 20 mg/CE 0.45 mg treatments were effective in endometrial protection after 12 months of treatment. In addition, both treatments showed significantly better effect on BMD than the placebo.

- Based on Study 305, BZA/CE treatments were effective in treatment of VMS. However, BZA 20 mg/CE 0.625 mg did not show significantly better effect than BZA 20 mg/CE 0.45 mg in reducing the average daily number of moderate to severe hot flushes, but it was a little better in reducing the severity (b) (4) of hot flushes .

Further analysis of Phase III data was performed by the pharmacometric team which revealed the following conclusions (see also **Appendix 4.3.1** for full analysis):

The BZA dose of 20 mg is the minimum effective dose among tested doses when combined with 0.45 or 0.625 mg CE. As stated above, low BZA dose of 10 mg failed to provide adequate endometrial protection, and higher BZA dose of 40 mg caused unacceptable efficacy loss.

With the exception of endometrial protection and improved tolerability, BZA did not show positive contribution to the three estrogenic efficacy endpoints (VMS, VVA, and PMO). Instead, it attenuated the desired treatment effect in a dose-dependent manner. Higher BZA doses were associated with greater estrogenic efficacy losses. When BZA dose was 40 mg, no significant difference was shown for VMS and VVA between BZA/CE and the placebo groups.

(b) (4)

(b) (4)

BZA 20 mg/CE 0.625 mg is not recommended [redacted] (b) (4)

Based on the above information and the known safety profiles of BZA, the exposure level relative to safety and efficacy appears to be narrow. From the clinical pharmacology perspective, there are three major challenges with this NDA as follows:

- Ensuring bridging of all formulations used in this NDA.
- Factors that may lower BZA exposure and inconsistency in absorption. Lowering BZA exposure or reduce absorption may be associated with safety concern due to lack of adequate endometrial protection.
- Factors that may increase BZA exposure are also associated with both safety and efficacy issues. The increase in BZA exposure may reduce CE efficacy (VMS, VVA, and BMD).

Therefore, consistency in BZA absorption, delivery, and systemic exposure appears to be critical in optimizing the long term therapy with this product.

2. Question Based Review

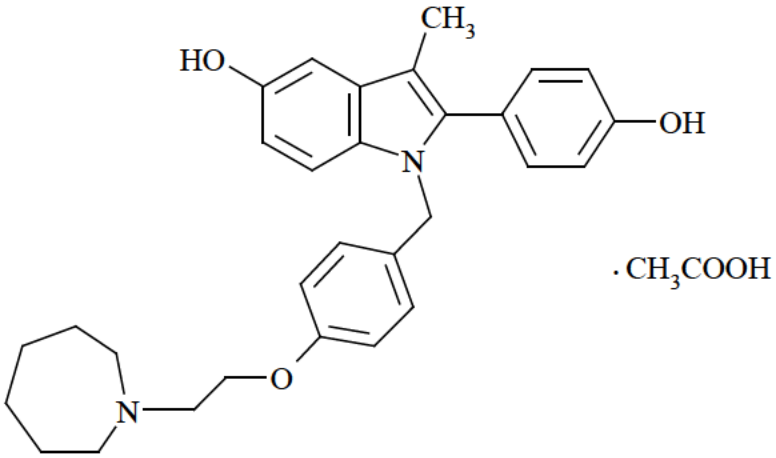
2.1 General Attributes/Background

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

For detail discussion of the formulation and drug product, please see the Biopharmaceutics Section 2.5.

(b) (4)

The empirical formula of BZA is $C_{30}H_{34}N_2O_3 \bullet C_2H_4O_2$, and the molecular weight is 530.65. BZA is a white to tan powder. The aqueous solubility of BZA is pH-dependent. Solubility is higher at lower pH. The following represents the chemical structure of BZA acetate:



Product Identification:

For clarity, BZA acetate refers to the active pharmaceutical ingredient in the drug product, and BZA refers to the analyte measured in plasma. CE refers to the mixture of the sodium salts of naturally-sourced estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate, and contains as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin, as well as a number of other estrogens,

progestins, androgens, and diverse molecules. CE is marketed as Premarin® in dosage strengths ranging from 0.3 mg to 1.25 mg. The BZA/CE product described in this NDA is formulated with 20 mg BZA and 0.45 mg or 0.625 mg CE.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.2.1 Mechanism of Action:

The mechanism of action will be reviewed by the pharmacology and toxicology team. However, according to the sponsor and our limited review of the available data, BZA and CE function by binding to and activating the two estrogen receptors (α and β). CE is composed of multiple estrogens that demonstrate tissue selective estrogen receptor agonist activity. BZA demonstrates both tissue estrogen receptor agonist and antagonist activity. The sponsor's theory is that BZA exhibiting agonist activity on the skeletal system, while acting as an estrogen antagonist in breast and uterine tissue.

Theoretically, for some endpoint measured such as vasomotor instability and BMD, the effect is a result of a combination of both components. The mainstay of the sponsors rationale of this combination is to maintain the effect of estrogen therapy (ET) for the treatment of VMS and VVA, and the prevention of PMO while certain estrogenic effects, such as stimulation of the uterus and breast are antagonized by BZA without the side effect associated to progestin containing HT.

In other word, BZA is replacing the progestin in the current CE/progestin combination therapy to improve endometrial safety.

2.1.2.2 Proposed Indications:

Loss of estrogen production in women during menopause results in a state of estrogen deficiency which has been associated with multiple symptoms, including VMS; symptoms of VVA; and difficulties with sleep, mood, memory, and sexual activity. In addition, estrogen deficiency has further been associated with loss of bone mass, which often leads to osteoporosis.

The only treatment option currently available to address multiple postmenopausal symptoms in women with an intact uterus (i.e., VMS, VVA, and the loss of bone mass leading to osteoporosis) is progestin-containing hormone therapy (HT). However, progestin-containing HT has been associated with vaginal bleeding and breast pain/tenderness, which are the most common reasons for discontinuation of treatment. In addition, women who use progestin containing HT are likely to have increases in breast density related to hormonal exposure.

Moreover, concerns surrounding side effects and published data regarding the association of progestin-containing HT with the increased risk for breast cancer have induced a decrease in the number of women seeking, initiating and continuing this type of therapy.

As stated earlier, it appears that BZA/CE therapy may provide an alternative to current HT (i.e., estrogen plus progestin [E+P]) for the management of menopausal health by offering the benefits of replacing estrogen, while minimizing the side effects and risks associated with E+P use.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

This application is being submitted to support the approval of 2 dosage strengths of BZA/CE tablets for once daily oral administration, BZA/CE 20 mg/0.45 mg and BZA/CE 20 mg/0.625 mg for the following indications:

- The treatment of VMS associated with menopause (BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg)
- The treatment of VVA associated with menopause (consider topical vaginal products when treating solely for vulvar and vaginal atrophy) (BZA 20 mg/CE 0.625 mg)
- The prevention of PMO (BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg).

2.1.3.1 What is the rationale for the proposed combination therapy?

As stated earlier, the rationale for the development of BZA/CE was that BZA, acting primarily as an estrogen receptor antagonist in uterine tissue, would inhibit the proliferative effects of CE on the endometrium in a manner mechanistically distinct from progestins, and therefore reduce the incidence of irregular uterine bleeding.

BZA acts primarily as an estrogen receptor antagonist in breast tissue, preventing the estrogenic stimulatory effect of CE in breast tissue, and therefore is poised not to induce breast pain or changes in breast density.

Potentially weighing against these benefits is an identified VTE risk based on the class effect of estrogens. According to the sponsor, the absolute VTE risk is likely to be small and not to exceed that observed with either CE or BZA therapies. However, such speculation will be assessed by the clinical team. Based on the results of clinical studies, the sponsor believes that the benefits outweigh the risks associated with BZA/CE treatment.

2.1.4. What are the (b) (4) studies submitted in this NDA?

This section lists the (b) (4) studies that have been submitted in this NDA. The most relevant clinical pharmacology, biopharmaceutics, and clinical studies are detailed in appropriate sections of this review and further in depth detail in the Individual Study Review Section (**4.2**).

Overview:

The Phase 1 program, consisting of 20 studies performed with BZA/CE and 15 studies performed with BZA, assessed the PK and PD properties of BZA and BZA/CE in generally healthy postmenopausal women. This Phase 1 program consisted of BA/BE, food effect, dose proportionality, drug interaction, and specific population studies. The studies were conducted using single or multiple doses of BZA ranging from 0.1 mg to 120 mg and doses of BZA/CE ranging from 10 mg to 40 mg of BZA with 0.45 mg and 0.625 mg of CE.

The BZA/CE clinical development program was initiated in 2001. Since that time, the sponsor has conducted a comprehensive clinical development program for BZA/CE, consisting of data from 26 clinical trials (20 Phase 1, 1 Phase 2, and 5 Phase 3 studies).

From the clinical pharmacology perspective, the sponsor conducted 24 clinical studies to support the BZA/CE clinical pharmacology program with BZA/CE or 1 of its components, BZA or CE. As stated above, there were 20 Phase 1 studies, of which 3 drug interaction and 2 other PK studies were specifically conducted for the BZA/CE program. PK data from one Phase 2 and three Phase 3 studies were also utilized for population PK analyses. All relevant studies described here are summarized in **Figure 2.1.4.1.**

It should be noted that each clinical study is identified by the project number prefix followed by a unique study number and a 2-letter country indicator suffix. The project number for the BZA monotherapy is **3068A1**; the project number for the BZA/CE development is **3115A1**. The monotherapy studies with the prefix 3068A1 (non-bold fonts) were previously submitted (b) (4)

These studies have already been reviewed by the Office of Clinical Pharmacology-OCP (see OCP original review dated August 17, 2006 (b) (4)). The 5 studies listed in **bold** in **Figure 2.1.4.1**were specifically conducted for the BZA/CE program.

Figure 2.1.4.1: Summary of BZA and BZA/CE Clinical Pharmacology Studies (n = 24)

Initial Safety, PK and PD	Drug Interactions	Drug Interactions	Exposure Response	ADME Biodistribution	Special Populations
SAD (3068A1-100-US)	Drug Interaction - Antacid (3068A1-102 FR)	**Drug Interaction-BZA/CE (3115A1-101-US)**	Population PK (3068A1-203-GL)	BZA ADME ^{14}C Radiolabel (3068A1-103-US)	Hepatic Disease (3068A1-112-EU)
MAD (3068A1-101-US)	Drug Interaction - Ibuprofen - (3068A1-106-SP)	**Drug Interaction-BZA on CE (3115A1-1134-US)**	Population PK (3068A1-300-GL)	BZA Absolute Bioavailability (3068A1-111-EU)	Age/Renal (3068A1-121-US)
BZA/CE Multiple Dose (3115A1-1138-US)	Drug Interaction - Azithromycin - (3068A1-125-EU)	**Drug Interaction-CE on BZA (3115A1-1135-US)**	QTc Study (3068A1-131-US)	BZA Dose Proportionality (3068A1-108-US)	SAD in China (3068A1-123-CI)
	Drug Interaction - Atorvastatin - (3068A1-126-EU)		Population PK (3115A1-303-US)	**BZA – BZA/CE Relative Bioavailability (3115A1-1136-US)**	SAD in Japan (3068A1-114-JA)
			Population PK (3115A1-304-WW)		MAD in Japan (3068A1-124-JA)

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; BZA = bazedoxifene; CE = conjugated estrogens; EU = Europe; FR = France; GL = global; JA = Japan; MAD = multiple ascending dose; PD = Pharmacodynamic; PK = Pharmacokinetic; QT_c = interval between the Q-wave and T-wave of the electrocardiogram, corrected; SAD = single ascending dose; US = United States; WW = worldwide

Note: Studies with the prefix 3068A1 were conducted with bazedoxifene monotherapy; studies with the prefix 3115A1 were conducted using BZA/CE. The studies conducted specifically for the BZA/CE development program are shown in **bold** font.

a. Four (4) studies listed in this figure were Phase 2 (3068A1-203-GL) or Phase 3 (3068A1-300-GL, 3115A1-303-US, and 3115A1-304-WW) studies that were used for population PK analyses.

Table 2.1.4.1: Design and Description of Clinical Pharmacology Studies

Type of Study Study Number	Description
Healthy Subject Pharmacokinetic and Initial Tolerability Studies	
3068A1-100-US	Ascending Single Dose (CSR-34914)
3068A1-101-US	Ascending Multiple Dose (CSR-35054)
3068A1-103-US	Mass Balance and Metabolism of [^{14}C]Bazedoxifene (CSR-35055)
3068A1-108-US	Dose Proportionality (CSR-45814)
3068A1-111-EU	Absolute/Relative Bioavailability of Bazedoxifene (CSR-40533)
3068A1-114-JA	Ascending Single Dose in Japanese Subjects (CSR-56881)
3068A1-123-CI	Ascending Single Dose in Chinese Subjects (CSR-40532)
3068A1-124-JA	Ascending Multiple Dose in Japanese Subjects (CSR-56882)
3068A1-131-US	Thorough QTc Study (CSR-62492)
3115A1-1138-US	BZA/CE Multiple-Dose Pharmacokinetics (CSR-78662)
3115A1-1136-US	Relative Bioavailability of Bazedoxifene Monotherapy and BZA/CE Combination Dosage Forms (CSR-78946)
Intrinsic Factor Pharmacokinetic Studies	
3068A1-112 EU	Hepatic Impairment (CSR-43639)
3068A1-121-US	Age and Renal Impairment (CSR-51806)
Extrinsic Factor Pharmacokinetic Studies	
3068A1-102-FR	Food Effect and Antacid Interaction (CSR-52314)
3068A1-106-SP	Ibuprofen Interaction (CSR-37791)
3068A1-125-EU	Azithromycin Interaction (CSR-56919)
3068A1-126-EU	Atorvastatin Interaction (CSR-50676)
3115A1-101-US	Conjugated Estrogens Interaction (CSR-46455)
3115A1-1134-US	Effect of Bazedoxifene on Conjugated Estrogens Pharmacokinetics (CSR-77064)
3115A1-1135-US	Effect of Conjugated Estrogen on Bazedoxifene Pharmacokinetics (CSR-77048)

Studies with the prefix 3068A1 were conducted with bazedoxifene; studies with the prefix 3115A1 were conducted using BZA/CE.

Reference ID: 3319890

Biopharmaceutics Studies:

Additionally, an extensive biopharmaceutics program with **15 studies** was undertaken by the sponsor, specifically related to formulation development. **Table 2.1.4.2** list all the biopharmaceutics studies submitted in this NDA.

These studies are discussed in more detail in appropriate sections of this review and specifically in the biopharmaceutics section **2.5** and Individual Study Review Section (**4.2**).

Table 2.1.4.2: Design and Description of Biopharmaceutics Studies

Type of Study (Location of CSR) Study Number and CSR Number	Study Objective(s)	Study Design and Type of Control	Test Product[a]; Dose Regimen; Route of Administration	Number of Subjects	Duration of Treatment[b]
Food-Effect Studies					
3115A1-102-US CSR-49949	Assess the effect of a high-fat meal on the relative bioavailability of BZA/CE; safety and tolerability.	Open-label, single-dose, randomized, 2-period crossover study.	BZA 40 mg/CE 0.625 mg fasting and after a high-fat meal. Oral	24	1 day
3115A1-1116-US CSR-69234	Assess the effect of a high-fat meal on the bioavailability of BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized-to-sequence, 3 period, crossover study.	BZA 20 mg/CE (PNP) 0.625 mg fasting or after a high-fat meal. BZA 20 mg/CE (PNP) 0.45 mg fasting. Oral	23	1 day
Comparative Bioavailability and Bioequivalence Studies					
3115A1-100-US CSR-45476	Compare the relative bioavailability of BZA and CE administered as separate tablets or as a combination-tablet formulation.	Open-label, single-dose, 3-treatment, 3-period, randomized crossover study.	BZA 10 mg x 4 and CE 0.625 mg BZA 10 mg/CE 0.625 mg BZA 40 mg/CE 0.625 mg Oral	24	1 day
3115A1-109-US CSR-62706	Assess the comparative bioavailability of 2 new formulations of BZA/CE (PNP) with BZA/CE (PCP) and with CE (PNP).	Open-label, single-dose, 4-period, crossover study.	BZA 40 mg/CE (PNP) 0.625 mg (b) (4) (Formulation B) BZA 40 mg/CE (PNP) 0.625 mg (b) (4) (Formulation B) BZA 40 mg/CE (PCP) 0.625 mg (Formulation A) CE (PNP) 0.625 mg Oral	24	1 day

3115A1-114-US CSR-67989	Assess the bioequivalence of BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized-to-sequence, 2 period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	72	1 day
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1117-US CSR-69737	Assess the bioequivalence of BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized, 4-period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation B) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) BZA 20 mg/CE (PNP) 0.625 mg (Formulation D [PCF]) Oral	76	1 day
3115A1-1120-US CSR-69235	Assess the bioequivalence between BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized, 3-period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	72	1 day
3115A1-1121-US CSR-69445	Assess subject exposure to BZA from 1 of 2 formulations of BZA 20 mg/CE 0.625 mg after steady-state administration.	Open-label, randomized, parallel inpatient/ outpatient study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	36 36	14 days
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1122-US CSR-75506	Assess the bioequivalence of clinical and commercial formulations of BZA/CE combination tablets.	Open-label, single-dose, randomized, 4-period, 4-treatment, crossover, bioequivalence inpatient/outpatient study.	BZA 20 mg/CE 0.625 mg (Formulation A - reference therapy). BZA 20 mg/CE 0.625 mg (Potential commercial formulation E - test formulation). BZA 20 mg/CE 625 mg (Potential commercial formulation F - test formulation). BZA 20 mg/CE 0.625 mg (Potential commercial formulation G – test formulation). Oral	82	1 day

Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1137-US CSR-77978	Bioequivalence of test and reference formulations of BZA/CE combination tablets, assessing both the BZA and CE components.	Open-label, single-dose, randomized, 4-period, 4-treatment, crossover study.	BZA 20 mg/CE 0.45 mg (Formulation A-reference therapy) BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). Oral	90	1 day
3115A1-1139-US CSR-76333	Assess the bioequivalence of clinical and commercial formulations of BZA/CE combination tablets, assessing both the BZA and CE components.	Open-label, single-dose, randomized, 2-period, 2-treatment, crossover study.	BZA 20 mg/CE 0.625 mg (Formulation B - reference therapy). BZA 20 mg/CE 0.625 mg (proposed TBM formulation - test formulation). Oral	90	1 day
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1142-US CSR-78945	Assess the bioequivalence of 4 formulations of BZA/CE.	Open-label, single-dose, randomized, 4-period, crossover study.	BZA 20 mg/CE 0.45 mg (Formulation B – reference formulation). BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). Oral	88	1 day
3115A1-1143-US CSR-77979	Assess the bioavailability of 3 test formulations of BZA/CE [redacted] compared with a potential market (reference) formulation of BZA/CE combination tablets, assessing only the BZA component.	Open-label, single-dose, randomized, 4-period, 4-treatment crossover study.	BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). BZA 20 mg/CE 0.45 mg (PCF - reference therapy) Oral	37	1 day
In Vitro/In Vivo Correlation Studies					
3115A1-115-US CSR-68097	Assess the bioavailability of BZA in [redacted] formulations of BZA/CE and an oral solution of BZA.	Open-label, single-dose, randomized, crossover study.	BZA 20 mg/CE 0.625 mg with the BZA component being: [redacted] BZA 20 mg powder for oral solution Oral	24	1 day
3115A1-1123-US CSR-72948	Bioavailability of BZA/CE.	Open-label, single-dose, nonrandomized, 4-period, crossover study.	[redacted] BZA 20 mg/CE 0.625 mg [redacted] BZA 20 mg/CE 0.625 mg [redacted] BZA 20 mg/CE 0.625 mg BZA 20 mg (oral solution) Oral	28	1 day

Clinical Trials:

Efficacy for the indications of the treatment of moderate-to-severe VMS associated with menopause, treatment of moderate-to-severe VVA associated with menopause, and the prevention of postmenopausal osteoporosis is supported by 4 Phase 3 pivotal trials and 1 Phase 3 supportive trial. Safety is supported by 5 Phase 3 clinical trials with 7271 women in the safety database overall, including 4868 women who were exposed to BZA/CE. Up to 2 years of safety data were collected in Studies 303 and 304. Full protocol numbers are listed in **Table 2.1.4.3**.

These studies are briefly described in Sections **2.4A and 2.4B**. However, for more detail assessment, interpretation, and analysis of the data you are referred to the Medical Officer's and biostatistics reviews.

Table 2.1.4.3: Overview of Phase 3 BZA/CE Clinical Development Program

Study FSFV-LSLV	n randomized	Duration	Study Description
303-US/EU/BR Apr 2002 to Jan 2006	n=3544	24 months	A Phase 3 multicenter, double-blind, randomized, placebo- and active-controlled safety and efficacy study evaluating the effect of 6 combinations of BZA/CE on the incidence of endometrial hyperplasia and the efficacy in preventing osteoporosis in postmenopausal women
304-WW Oct 2005 to Aug 2008	n=1083	12 months	A Phase 3 multicenter, double-blind, randomized, placebo- and active-controlled efficacy and safety study evaluating BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg for endometrial safety and the prevention of osteoporosis.
	n=523	12 months[a] (Total duration=24 months)	
305-US Sep 2005 to Feb 2007	n=332	12 weeks	A Phase 3 multicenter, double-blind, randomized, placebo-controlled, efficacy and safety study designed to demonstrate the efficacy of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg in the treatment of moderate to severe VMS.
306-WW Oct 2005 to Mar 2007	n=664	12 weeks	A Phase 3 multicenter, double-blind, randomized, placebo- and active-controlled efficacy and safety study designed to assess the efficacy of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg in VVA.
3307-WW Jan 2009 to Feb 2011	n=1886	12 months	A Phase 3, multicenter, double-blind, randomized, placebo- and active-controlled efficacy and safety study evaluating BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg for endometrial safety and the prevention of osteoporosis.

Abbreviations: BR=Brazil; BZA=bazedoxifene; CE=conjugated estrogens; EU=European Union; FSFV=first subject first visit; LSLV=last subject last visit; n=number of subjects; US=United States; VVA=vulvar-vaginal atrophy; WW=world-wide

a. Study 304 extension study was a 12 month study added by protocol amendment with the objective to collect additional efficacy and safety data for an additional 12 months after the initial 12 month study; total duration of Study 304 was 24 months.

In addition, the sponsor included in this application the safety and efficacy data from the Phase 2 and Phase 3 clinical studies conducted with BZA monotherapy (b) (4)

2.1.4.1 What is known of the BZA PK (synopsis of monotherapy PK program)?

As stated earlier, the PK of BZA was reviewed (b) (4) (b) (4) the following is a summary of the BZA PK profiles and characteristics:

Absorption (Biopharmaceutics)

- A 20 mg BZA tablet is absorbed from the gastrointestinal tract and its mean Cmax and tmax are 6.2 ng/mL and 1.7 hours, respectively, at steady state. A secondary peak appears in the plasma BZA concentration-time profiles.
- A high fat meal increases BZA Cmax and AUC by 77 and 71%, respectively following 40 mg BZA tablet.
- BZA absolute oral BA is approximately 6% using the mono-formulation at that time. However, there is no information on the absolute BA for the combination product. But it is anticipated to still be low and not much too far from the mono-formulation.
- BZA PK is dose-proportional for oral single doses from 2.5 to 120 mg and for oral multiple daily doses from 5 to 80 mg.
- Plasma BZA concentrations at steady state are about 2 times those after a single dose.

Distribution

- The mean BZA volume of distribution is 14.7 L/kg.
- BZA is 95.8 – 99.3% plasma protein bound.
- BZA does not affect warfarin, diazepam, or digoxin's plasma protein binding.
- Warfarin, diazepam, or digoxin does not affect BZA plasma protein binding.
- Blood/plasma ratios of radioactivity from administered C^{14}-BZA are below 0.55.

Metabolism

- BZA is extensively metabolized to the phenyl and indole glucuronides with little or no oxidative metabolism.
- The indole glucuronide is the major circulating metabolite, whereas the phenyl and di-glucuronides are the minor metabolites in plasma. The ratios of plasma indole glucuronide concentration to plasma BZA concentration are about 11.7-16.6.
- UGT1A1 and UGT1A10 metabolize BZA to its phenyl and indole glucuronides.
- The indole metabolite may contribute to 6.7-9.5% of BZA *in vivo* antagonistic activity at the receptors.

Excretion

- The mean radioactive dose recovered in feces and urine over 10 days postdose was 84.7 and 0.81%, respectively. More than 90% of the recovered radioactive dose in feces belongs to unchanged BZA.

- Partial hydrolysis (20-40%) of BZA glucuronides to BZA occurred in spiked fecal samples. Biliary clearance for the phenyl glucuronide may be higher than that for the indole glucuronide.
- BZA half-life at steady state is approximately 30 hours.

Pharmacodynamics

- BZA has effect on lumbar spine BMD.
- The effect on BMD appears to be dose dependent over 10, 20, and 40mg daily doses over 24 month treatment compared to placebo.
- VTE are the primary safety concern for BZA.

QT Prolongation

- Single oral doses of 20 and 120 mg BZA do not prolong QTc intervals per a thorough QT study.

Specific Populations

- Severe renally impaired (CrCl < 30 mL/min) postmenopausal patients' (n = 2) BZA AUC increased 69% as compared to that of 8 healthy postmenopausal women (51-64 years) when they received a 20 mg single oral BZA dose.
- The mid-elderly (65-74 years) group and elderly (> 75 years) group's BZA AUCs increased 54 and 158% from that of the young-elderly (51-64 years) group when they received a 20 mg single oral BZA dose.
- The disposition of a 20 mg single oral BZA dose is examined in patients with different hepatic impairments (Child-Pugh Class A, B, and C) and healthy participants. Patients with mild, moderate, and severe hepatic impairment showed 143, 109, and 268% increase, respectively, in BZA AUCs as compared to that for healthy participants.
- Race does not appear to affect BZA PK.

Drug-Drug Interactions

- BZA and ibuprofen PK are not significantly altered upon co-administration of single oral doses of these 2 drugs.
- There was no noticeable interaction between BZA and atorvastatin.
- BZA AUC (oral 40 mg dose) decreases 15% in the presence of oral 250 mg azithromycin.
- A single dose of antacids containing 460 mg aluminum hydroxide and 400 mg magnesium hydroxide has no effect on a single oral 40 mg BZA dose.

Biopharmaceutics

- In addition to the absorption information mentioned earlier, BZA acetate is considered according to the biopharmaceutics classification system (BCS) is to exhibit low solubility drug.
- There is not enough data to classify BZA acetate as a BCS high permeability drug.
- (b) (4)

2.2 General Clinical Pharmacology

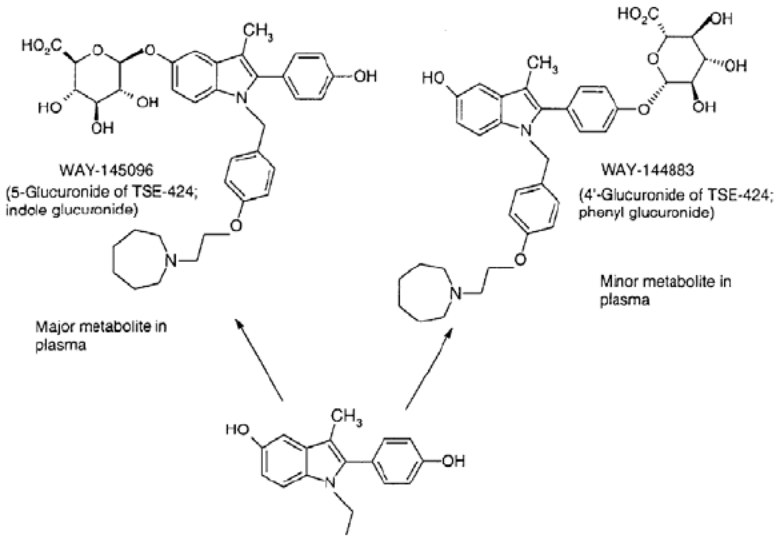
2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contributes to the assessment of clinical pharmacology study data? How were they measured?

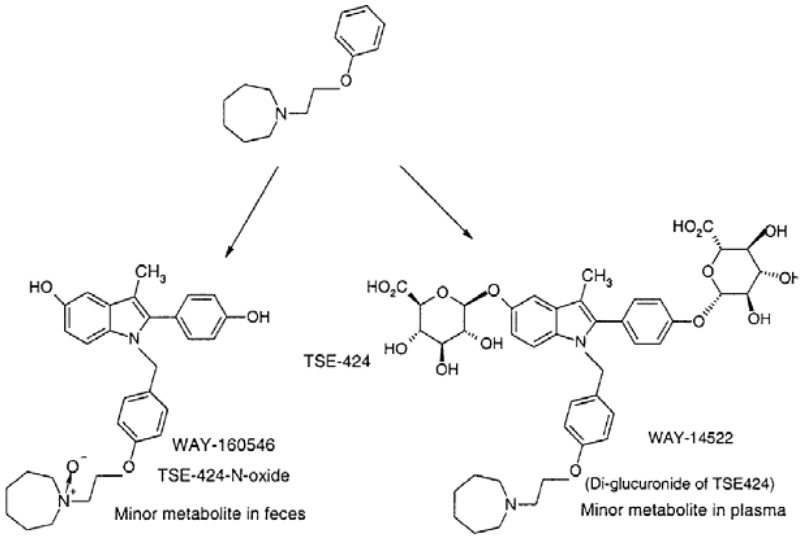
See Phase III/clinical trials summary (Section 2.4 A) followed by pharmacometric analysis (Section 2.4 B).

2.2.2 What are the Characteristics of Drug Metabolism?

The metabolism of BZA/CE combination tablet has not been studied. Based upon Phase I studies conducted with the BZA alone tablet in the monotherapy program, BZA is extensively metabolized in humans (b) (4)
The indole glucuronide constituted 40 to 95% of radioactivity in plasma at all time points.

Figure 2.2.2.1: Metabolic Pathways of BZA in Humans





2.2.3 Does this Drug Prolong the QT or QTc Interval?

Based on single doses of 20 and 120 mg of BZA there was no evidence of QTc prolongation per a thorough QT study.

2.2.4 What are the PK characteristics of the drug?

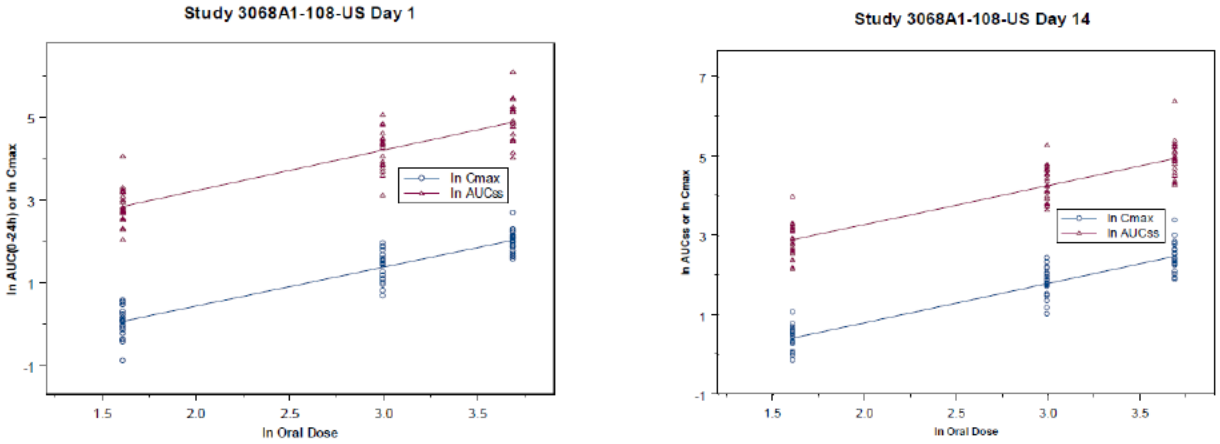
The following discussion is primarily focus on the PK of BZA and selective CE components whenever applicable.

2.2.4.1 What are the single and multiple dose PK parameters of BZA and its metabolites? How do the PK parameters change with time following chronic dosing?

From the monotherapy program, the exposure of BZA is dose proportional following single doses of ranging from 2.5 mg to 120 mg and multiple doses of 5 to 80 mg. The BZA exposure at steady-state appears to be about twice of that after a single dose (Study 100-US, see clinical pharmacology Review dated March 21, 2007, Page 11).

From the clinical pharmacology review **Figure 2.2.4.1.1** shows the Cmax and AUC on Day 1 and day 14 following 5, 20, and 2x20 (40 mg) BZA tablets. From this study the exposure Cmax and AUC on Day 14 are consistently higher compared to Day 1. Also, this figure shows dose proportionality over 5 to 40 mg BZA single dose and multiple doses.

Figure 2.2.4.1.1: Cmax and AUC on Day 1 and Day 14 of 5, 20, and 2 x 20 mg BZA Tablets (Study 108-US, (b) (4)).



A similar conclusion in terms BZA exposure was also reached for the combination therapy for BZA/CE. The exposure (Cmax and AUC) was about twice higher after 10 days of multiple doses of 20mg/0.45 mg compared to single doses (**Figure 2.2.4.1.2 and Table 2.2.4.1.1**, Study 3115A1-1138-US).

Figure 2.2.4.1.2: BZA Plasma Concentration-Time Profiles on Day 1 and Day 10 of 20/0.45 mg BZA/CE (Study 1138)

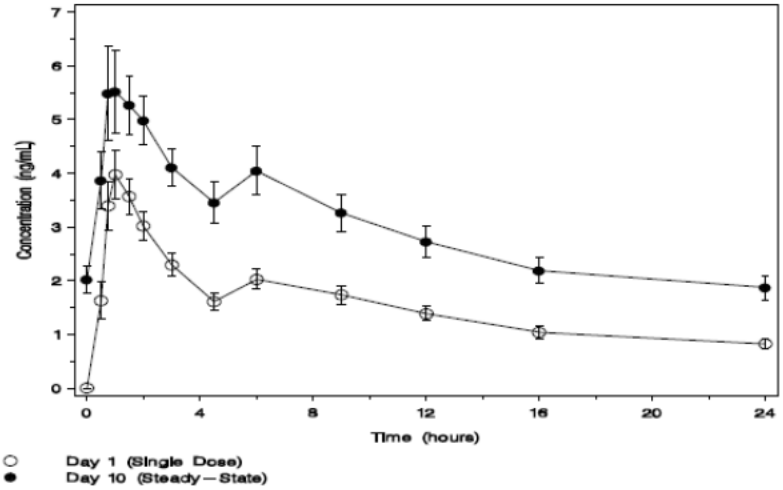


Table 2.2.4.1.1: PK Parameters on Day 1 and Day 10 (Study 1138-US)

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)

Furthermore, the exposure of CE components was also increased by approximately two times on Day 10 compared to Day 1 in the same study. **Figure 2.2.4.1.3 and Table 2.2.4.1.2** 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.

Figure 2.2.4.1.3: Plasma concentration-Time Profiles of Unconjugated Estrone Following the Administration of 20/0.45 mg BZA/CE (Study 1138-US)

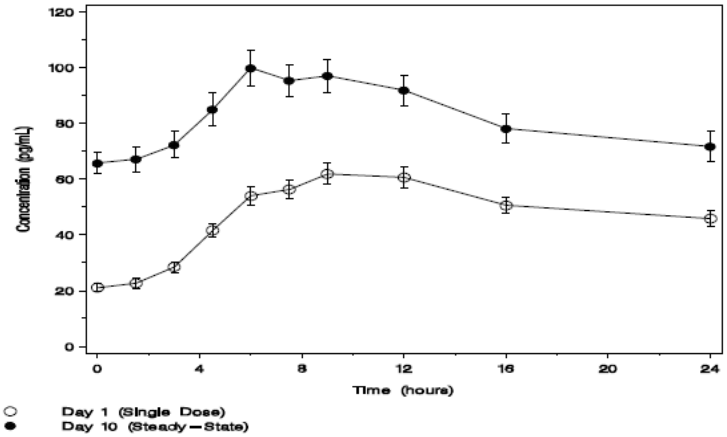


Table 2.2.4.1.2: Plasma concentration-Time Profiles of Unconjugated Estrone Following the Administration of 20/0.45 mg BZA/CE (Study 1138-US)

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)

It can be concluded that from both monotherapy and combination programs the BZA exposure is consistently twice after multiple doses compared to single dose. The same conclusion can be made for CE components.

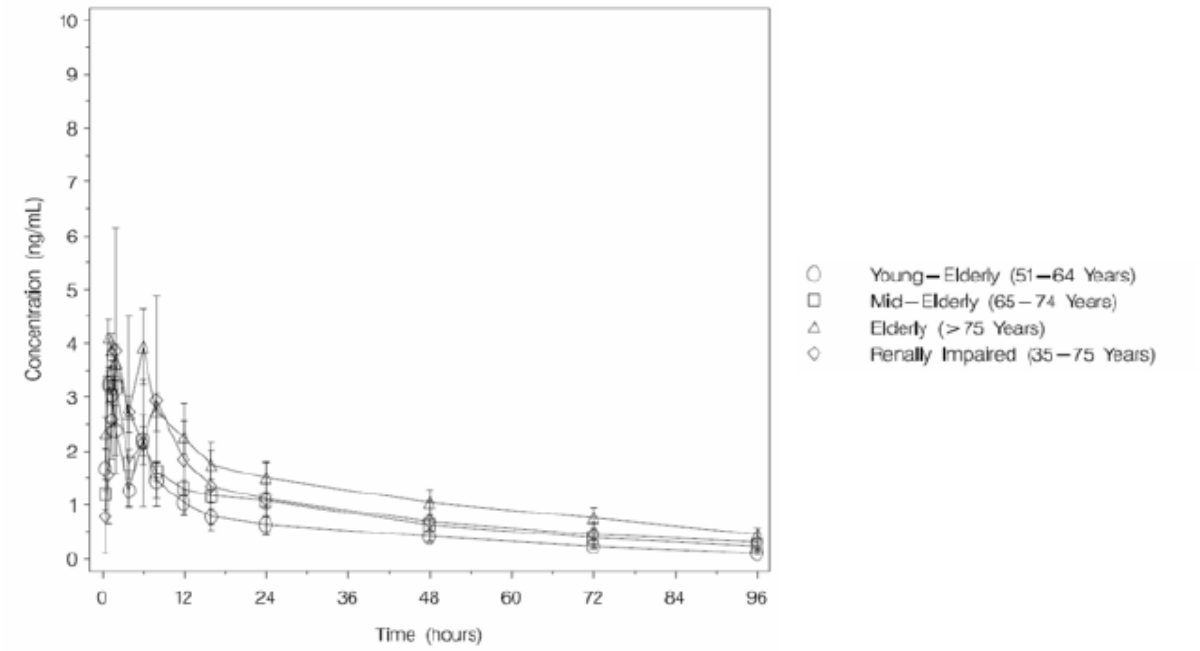
2.3 Intrinsic factors

2.3.1 Does age, race, or organ dysfunction affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 Effect of Age:
The applicant evaluated the effect of age on the PK of BZA in a non-randomized, single-dose, open-label study following a 20 mg BZA tablet after a 10-hr fast ((b) (4) Study 121-US). Postmenopausal women were stratified into three age groups: young-elderly (51 to 64 yrs; n=8), mid-elderly (65 to 74 yrs; n=8), and elderly (>75 yrs; n=8).

Compared to young-elderly patients, mid-elderly and elderly postmenopausal patients showed a 54% and 158% increase in BZA AUC, respectively. Arithmetic mean Cmax and half-life were similar at 3.8 ng/mL and ~31 to 32 hrs, respectively, for the young- and mid-elderly women. However, Cmax increased by 34% and half-life was prolonged from 32 hrs to 46 hrs in the elderly, compared to the young-elderly patients. Clinical Pharmacology Reviewer of BZA monotherapy NDA (b) (4) states that glucuronidation is not affected by aging.

The following figure is the plasma concentration-time profile of BZA in elderly postmenopausal women following a single 20 mg dose of BZA ((b) (4) Study 121-US).



The following table summarizes the PK parameters of BZA in elderly postmenopausal women following a single 20 mg dose of BZA (data from (b) (4) Study 121-US).

Group		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
Young-elderly	Mean±SD	3.76±1.23	2.3±2.3	32.0±5.7	52.1±26.0	59.2±28.7
	%CV	32.8	99.4	17.7	49.9	48.4
	n	8	8	8	8	8
	Geometric Mean	3.57	1.6	31.5	46.8	53.5
	(Range)	(1.94 to 5.40)	(0.5 to 6.0)	(20.6 to 38.0)	(21.2 to 102)	(24.9 to 113)
Mid-elderly	Mean±SD	3.87±1.67	2.5±2.2	30.7±6.9	76.1±24.6	87.4±32.4
	%CV	43.2	87.5	22.5	32.3	37.0
	n	8	8	8	8	8
	Geometric Mean	3.65	1.9	30.0	72.5	82.1
	(Range)	(2.73 to 7.83)	(1.0 to 6.0)	(18.8 to 39.6)	(42.7 to 110)	(45.2 to 139.2)
Elderly	Mean±SD	5.03±1.18	2.4±2.2	45.6±25.5	121±59.7	157±79.2
	%CV	23.4	91.4	55.9	49.5	50.6
	n	8	8	8	8	8
	Geometric Mean	4.94	1.8	40.8	109	138
	(Range)	(4.24 to 7.84)	(1.0 to 6.0)	(19.7 to 104)	(58.4 to 233)	(62.3 to 294)

For the treatment of VMS, the sponsor enrolled postmenopausal women with a mean age of 53 yrs (range: 42 to 64 yrs) in Phase III Study 305. For the treatment of VVA, the sponsor enrolled postmenopausal women with a mean age of 56 yrs (range: 41 to 65 yrs) in Phase III Study 306. For the treatment of PMO, the sponsor enrolled postmenopausal women with a mean (SD) age of 56 yrs (5.8) yrs in the 1-yr Study 3307 and postmenopausal women with a mean age of 54 yrs (range: 43 to 64 yrs) in the 2-yr Phase III Study 303. The applicant states in section 2.6 of the proposed label, that BZA/CE has not been studied in women over 75 yrs. The applicant states that in 224 women included in clinical trials, between 65 and 75 yrs, no dosage adjustment was required. Due to the lack of information from the Phase 3 studies and the 2.6-fold increase in BZA exposure in the elderly women compared to the younger women from (b) (4) Study 121-US, use of BZA/CE in elderly women (>75 yrs) is not recommended.

2.3.1.2 Effect of Renal Impairment

The applicant evaluated the effect of renal impairment as part of the age-effect study ((b) (4) Study 121-US). In males, age 35 to 75 yrs old, with severe renal impairment (CLcr: 24 - 52 mL/min; N=2), Cmax and AUC of BZA increased by 81% and 14%, respectively, compared to the young-elderly patients (51 to 64 years old) According to FDA's Draft Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010), patients with a CLcr of 24 - 52 mL/min would be considered to have moderate to severe renal impairment. Moderate renal impairment is classified by a CLcr of 30 - 59 mL/min and severe renal impairment is categorized by a CLcr of 15 - 29 mL/min. Due to the low number of subjects (N=2) and wide age range (35 - 75 yrs) in the renal impairment group, it is not possible to conclude that renal impairment affects BZA exposure. The sponsor did not provide an acceptable evaluation of renal impairment on BZA and CE exposure.

The sponsor excluded enrollment of patients with renal impairment in all of the Phase III studies and did not conduct a dedicated Phase I PK study in renal impairment patients. Therefore, the effect of renal impairment on clinical outcome and BZA PK are unknown.

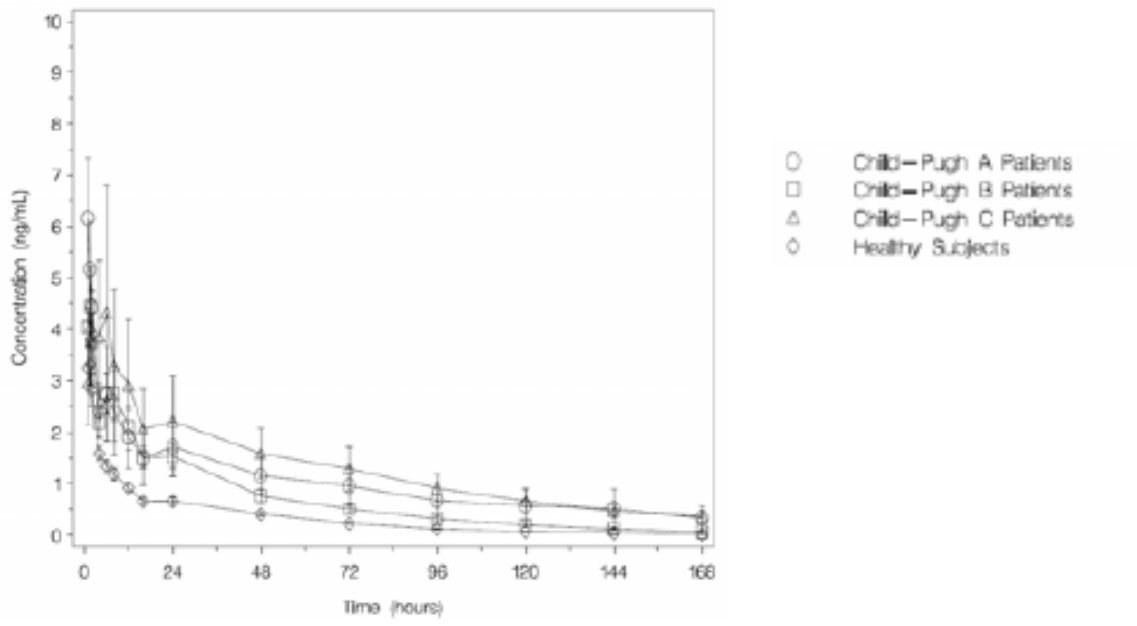
The following table summarizes the PK parameters of BZA in young-elderly patients (N=8) and men (N=2) with severe renal impairment following a single 20 mg dose of BZA (data from (b) (4) Study 121-US).

Group		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
Young-elderly	Mean±SD	3.76±1.23	2.3±2.3	32.0±5.7	52.1±26.0	59.2±28.7
	%CV	32.8	99.4	17.7	49.9	48.4
	n	8	8	8	8	8
	Geometric Mean (Range)	3.57 (1.94 to 5.40)	1.6 (0.5 to 6.0)	31.5 (20.6 to 38.0)	46.8 (21.2 to 102)	53.5 (24.9 to 113)
Renal Impairment	Mean±SD	4.30±2.61	1.5±0.7	42.2±7.3	89.1±70.1	107±80.3
	%CV	60.8	47.1	17.4	78.6	75.3
	n	2	2	2	2	2
	Geometric Mean (Range)	3.88 (2.45 to 6.15)	1.4 (1.0 to 2.0)	41.9 (37.0 to 47.4)	74.1 (39.6 to 139)	90.3 (49.9 to 164)

2.3.1.3 Effect of Hepatic Impairment

In a non-randomized, single-dose, open-label study conducted with BZA 20 mg alone tablets in fasted, healthy and hepatically impaired postmenopausal women ((b) (4) Study 112-EU), patients with mild hepatic impairment had Cmax and AUC of BZA increase by 67 and 143%, respectively, as compared to those of healthy subjects. Patients with moderate hepatic impairment had Cmax and AUC of BZA increase by 32 and 109%, respectively, as compared to those of healthy subjects. Patients with severe hepatic impairment had Cmax and AUC of BZA increase by 20 and 268%, respectively, as compared to those of healthy subjects. Compared to healthy subjects, half-life was significantly prolonged from 32 hrs to 50 hrs in patients with severe hepatic impairment (Child Pugh Class C).

The following figure is the plasma concentration-time profile of BZA in subjects with hepatic impairment and in healthy subjects (Study 112-EU).



The following table summarizes the PK parameters of BZA for subjects with normal hepatic function and patients with mild, moderate and severe hepatic impairment (data from study 112-EU).

Group		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Child-Pugh A subjects	Mean±SD	6.16±2.89	1.1±0.2	37.5±25.3	169±156	205±221
	%CV	46.9	18.8	67.5	92.1	108
	N	6	6	6	6	6
	Geometric mean	5.66	1.1	32.6	119	130
	(Range)	(3.60-10.2)	(1.0-1.5)	(20.3-87.5)	(49.2-413)	(50.6-599)
Child-Pugh B subjects	Mean±SD	4.76±1.74	2.6±2.7	34.6±1.6	114±38.8	118±40.2
	%CV	36.5	103	4.6	34.1	34.0
	N	6	6	6	6	8
	Geometric mean	4.49	1.9	34.5	108	112
	(Range)	(2.50-7.31)	(1.0-8.0)	(32.8-37.2)	(59.2-172)	(61.3-177)
Child-Pugh C subjects	Mean±SD	5.44±5.55	2.8±1.8	49.7±5.7	215±181	241±202
	%CV	102	63.8	11.5	84.2	83.7
	N	6	6	6	6	6
	Geometric mean	4.09	2.4	49.4	175	196
	(Range)	(2.10-16.6)	(1.5-6.0)	(41.5-57.0)	(94.6-575)	(110-642)
Healthy subjects	Mean±SD	3.76±1.64	1.9±1.4	32.0±9.4	54.8±18.9	56.4±19.0
	%CV	43.5	71.7	29.2	34.5	33.7
	N	18	18	18	18	18
	Geometric mean	3.40	1.6	31.0	51.7	53.4
	(Range)	(1.13-6.66)	(1.0-6.0)	(20.1-62.2)	(27.5-91.4)	(29.1-93.8)

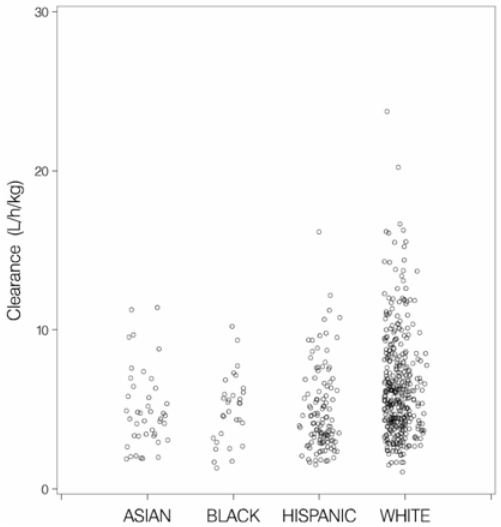
All degrees of hepatic impairment increased BZA exposure by 2-fold or more. Based upon exposure-response analysis for VMS, the beneficial effects from CE in reducing frequency and severity of hot flushes and spinal BMD were reduced when BZA exposure increased. The attenuating effects of BZA on CE were particularly profound when the BZA dose increased from 20 to 40 mg. Additional endometrial protection was not gained by increased BZA doses when used in combination with CE. From the BZA monotherapy program, doubling the BZA dose from 20 to 40 mg did not improve BMD. Overall, hepatic impairment resulted in an increase in BZA exposure and can subsequently negate the beneficial effects of CE.

Additionally, the sponsor excluded enrollment of patients with hepatic impairment in all of the Phase III studies; therefore, the effect of hepatic impairment on clinical safety is unknown. The sponsor proposes to contraindicate the use of BZA/CE in patients with liver dysfunction or disease. Because the benefits of CE are attenuated with increased BZA exposure and there are no data on the safety of BZA/CE use in patients with hepatic impairment, BZA/CE is not recommended for use in patients with hepatic impairment.

2.3.1.4 Effect of Race

The sponsor did not directly evaluate the effect of race/ethnicity on BZA exposure. The sponsor evaluated the effect of race by pooling weight-adjusted BZA clearance values from 437 postmenopausal women of different race/ethnic backgrounds (41 Asian, 26 black, 80 Hispanic, and 290 white) (b) (4) The sponsor did not disclose which studies were pooled to obtain the data for the figure below. White patients appear to have slightly higher weight-adjusted clearance values than the other ethnic groups. Patients of Asian (Chinese), Black and Hispanic descent had similar weight-adjusted BZA clearance values.

The following figure is weight-adjusted clearance of BZA vs. race/ethnic origin in clinical pharmacology studies (b) (4)



The following table summarizes the BZA CL/F values for postmenopausal women of different race/ethnic background enrolled in 4 PK studies following BZA alone administration (b) (4)

Ethnicity (n)	Median Bazedoxifene CL/F (range) L/h/kg	Study
White only (31)	7.1 (2.7 – 16.2)	126-EU
Chinese only (60)	4.69 (1.89 – 11.4)	123-CI
White (27)	5.94 (2.2 – 10.4)	125-EU
Hispanic (3)	11.8 (6.5 – 15.5)	125-EU
Black (14)	4.02 (2.51 – 7.30)	127-US
White (14)	5.42 (2.67 – 9.44)	127-US

With only 3 subjects in the Hispanic group, it is unclear if patients of Hispanic origin would have a different BZA exposure compared to the others.

Race/ethnicity does not appear to have an effect on BZA PK.

2.4 Extrinsic factors

2.4.1 What extrinsic factors such as drugs influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

See drug-drug interaction Section.

2.4.1.1 What is the Effect of Other Drugs on BZA?

Effect of CE on BZA PK

In an open-label, single/multiple-dose, non-randomized, 3-period, crossover study in healthy postmenopausal women, the sponsor evaluated the potential PK interaction of multiple oral doses of CE and a single dose of BZA (NDA 022247, Study 3115A1-1135-US). subjects received all 3 treatments in the order shown below:

Treatment A (period 1): Single dose of a BZA 20 mg tablet

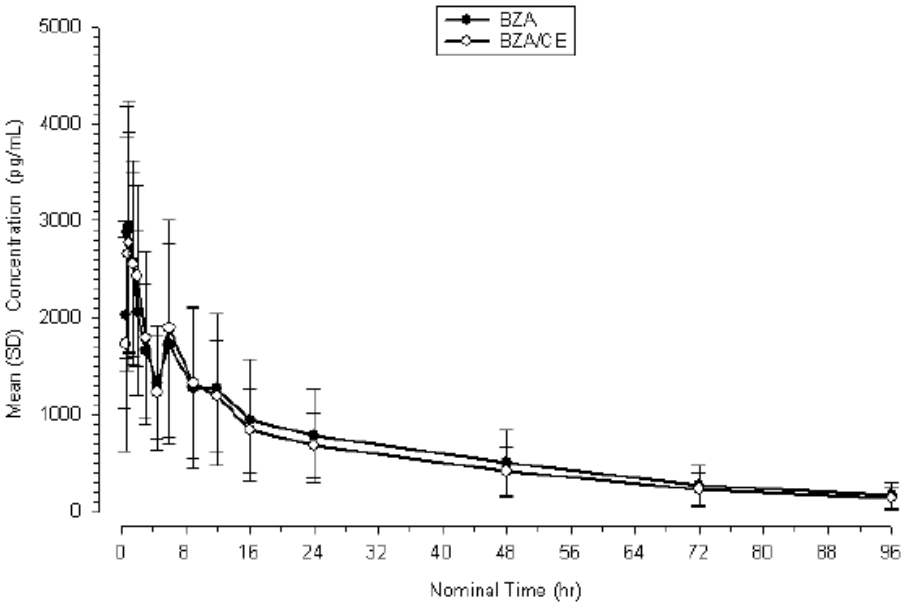
Treatment B (period 2): Once daily administration of a CE 0.625 mg tablet for 5 days

Treatment C (period 3): Single dose of a BZA 20 mg tablet and once daily administration of a CE 0.625 mg tablet for 4 days (for CE: 1 dose prior to BZA administration on Day -1, 1 dose with BZA on Day 1, and 2 doses thereafter on Days 2 and 3)

On Day 1 of period 1, each subject received a single oral dose of a BZA 20 mg tablet. On Day 1 of period 2 through Day 3 of period 3, each subject received a CE 0.625 mg tablet once daily. On Day 1 of period 3, a single oral dose of a BZA 20 mg tablet was co-administered with the CE 0.625 mg tablet.

A comparison of a single dose of BZA following multiple doses of CE and BZA alone showed the geometric mean ratio (90% CI) for Cmax, AUC_{0-96}, and AUC_{0-inf} were 1.03 (88-121%), 0.97 (78-121%), and 0.94 (76-117%), respectively. BZA exposure after a single dose administration was not significantly affected by multiple doses of CE suggesting that CE does not affect BZA BA.

The following are concentration-time profiles of BZA following a single dose of BZA 20 mg alone and single dose of BZA 20 mg with multiple doses of CE 0.625 mg (NDA 022247, Study 3115A1-1135-US).



The following is a summary of mean ± SD PK parameters of BZA following a single dose of BZA 20 mg alone and a single dose of BZA 20 mg with multiple doses of CE 0.625 mg ((NDA 022247, Study 3115A1-1135-US).

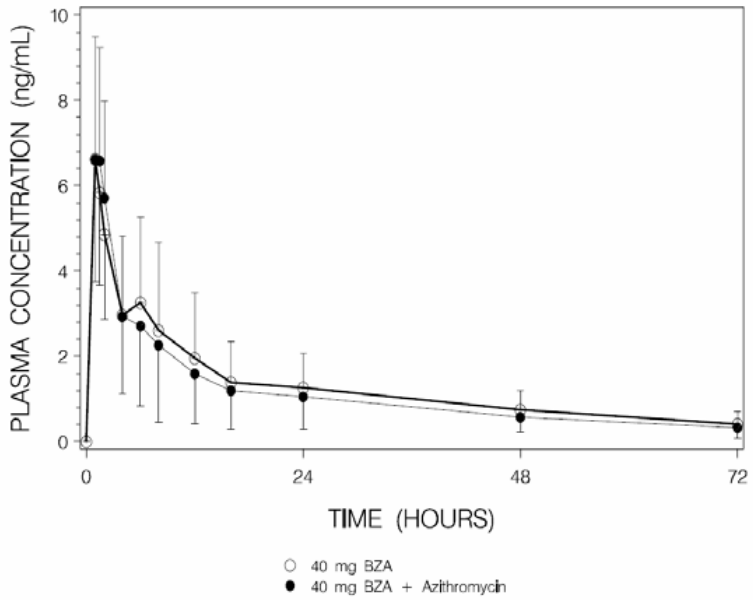
	Treatment	
Mean±SD	**BZA**	**BZA/CE**
N	30	29
C_{max} (ng/mL)	3.33±1.29	3.35±1.04
t_{max} [a] (h)	1.00 (0.50-12.00)	1.00 (0.50-9.00)
$t_{1/2}$ (h)	27.90±7.17	28.54±8.52
AUC_T (ng•h/mL)	59.0±33.9	54.9±25.8
AUC (ng•h/mL)	66.5±39.1	61.1±31.3

Effect of Azithromycin on BZA PK

In a non-randomized, open-label, sequential study, the applicant evaluated the effect of multiple doses of azithromycin on BZA PK following a single 40 mg dose of in 30 healthy postmenopausal women ((b) (4) Study 125-EU). Each subject received a 40 mg BZA oral tablet on Day 1 alone and on Day 13 with 250 mg azithromycin; BZA was taken after a 10-hr fast. On Day 9 each subject received 2 x 250 mg azithromycin tablets and 1 x 250 mg azithromycin tablet daily on Days 10 to 13. Azithromycin was taken under fast on Day 13; otherwise it could be taken without respect to food intake.

For Cmax of BZA, the 90% CI ratio of BZA + azithromycin/BZA alone fell within the BE limits of 80 - 125%. AUC of BZA decreased by 15% and would in most cases be considered insignificant; however, the 90% CI ratio was outside the BE limit (78% – 93%).

The following figure presents the mean plasma BZA concentration-time profiles following a single BZA 40 mg tablet alone and a single BZA 40 mg tablet + multiple doses of azithromycin ([redacted] Study 125-EU).



The following table summarizes the PK parameters of BZA following a single BZA 40 mg tablet alone and a single BZA 40 mg tablet + multiple doses of azithromycin ([redacted] Study 125-EU).

Treatment	C_{max} (ng/mL)	C_{max} GLSMR	90% CI C_{max} GLSMR	AUC (ng.h/mL)	AUC GLSMR	90% CI AUC GLSMR
40 mg BZD (reference)	6.5			99		
40 mg BZD + azithromycin	6.9	106	97 - 117	84	85	78 - 93

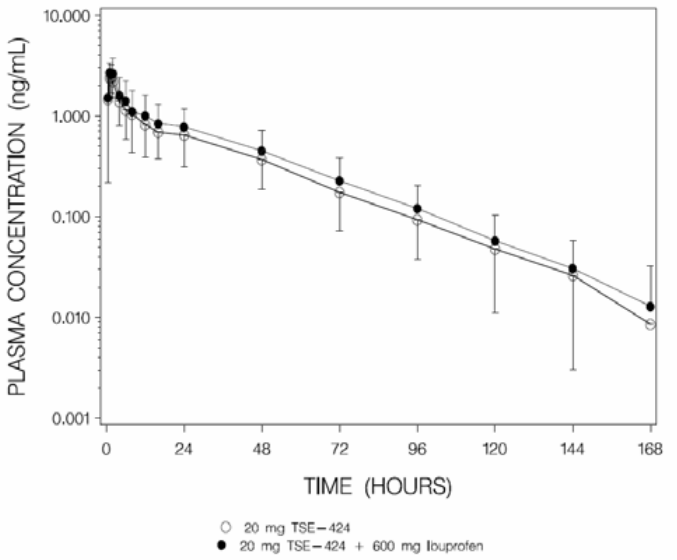
Effect of Ibuprofen on BZA PK

In an open-label, randomized, single-dose, 3-way, crossover study in 12 healthy postmenopausal women, the applicant evaluated the potential interaction between BZA and ibuprofen ([redacted] Study 106-SP). Each subject fasted for 10 hrs and received the following 3 treatments in 3 periods with at least 14 days washout period between treatments:

- a 600 mg ibuprofen tablet
- a 20 mg BZA capsule
- a 600 mg ibuprofen tablet + a 20 mg BZA capsule

BZA Cmax and AUC were increased by 18% and 7%, respectively, when a single dose of BZA 20 mg capsule was given with a single dose of 600 mg ibuprofen.

The following figure presents the mean plasma BZA concentration-time profiles following a single BZA 20 mg capsule alone and a single BZA 20 mg capsule + single dose of ibuprofen 600 mg tablet ([redacted] Study 106-SP).



The following table summarizes the PK parameters of BZA following a single BZA 20 mg capsule alone and a single BZA 20 mg capsule + single dose of ibuprofen 600 mg tablet ((b) (4) Study 106-SP).

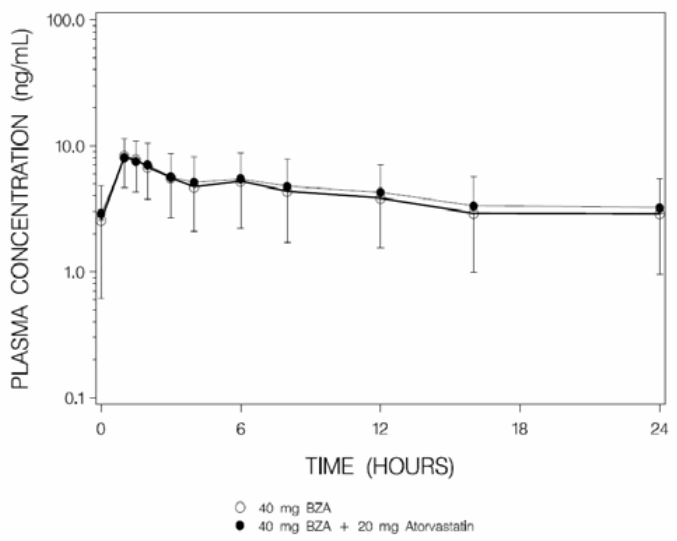
Treatment	C_{max} (ng/mL)	C_{max} GLSMR	90% CI C_{max} GLSMR	AUC (ng.h/mL)	AUC GLSMR	90% CI AUC GLSMR
20 mg BZD (reference)	2.5			47.4		
20 mg BZD + ibuprofen	2.9	118	96 - 144	50.2	107	85 - 134

Effect of Atorvastatin on BZA PK

In a non-randomized, open-label, sequential study in 30 healthy postmenopausal women, the applicant evaluated effect of single 20 mg oral dose of atorvastatin on multiple doses of 40 mg BZA PK ((b) (4) Study 126-EU). Each subject received a single 20 mg atorvastatin dose alone on Day 1 and on Day 12 with 40 mg BZA. On Days 4 - 12, each subject received 9 consecutive daily 40 mg BZA doses. On Days 1, 11, and 12 (PK samples collection), subjects took the treatment drugs after a 10-hr fast.

BZA Cmax and AUC following multiple daily oral doses of 40 mg BZA was not affected by a single oral dose of 20 mg atorvastatin. Geometric mean ratios for BZA AUC and Cmax were 1.06 and 0.97, respectively.

The following figure presents the mean plasma BZA concentration-time profiles following a single BZA 40 mg alone and a single dose of atorvastatin 20 mg + multiple doses of BZA 40 mg ((b) (4) Study 126-EU).



The following table summarizes the PK parameters of BZA following BZA 40 mg alone with and without atorvastatin ((b) (4) Study 126-EU).

Treatment	C_{max} (ng/mL)	C_{max} GLSMR	90% CI C_{max} GLSMR	AUC (ng.h/mL)	AUC GLSMR	90% CI AUC GLSMR
40 mg BZD (reference)	8.2			86.6		
40 mg BZD + atorvastatin	8.0	97	91 - 104	91.6	106	101 - 111

2.4.1.2 What is the Effect of BZA on Other Drugs?

Effect of BZA on CE PK

In an open-label, single/multiple-dose, non-randomized, 3-period, crossover in healthy postmenopausal women, the applicant evaluated the potential PK interaction of multiple oral doses of BZA and a single dose of CE when co-administered (NDA 022247, Study 3115A1-1134-US). Subjects received all 3 treatments in the order shown below:

Treatment A (period 1): Single dose of a CE 0.625 mg tablet

Treatment B (period 2): Once daily administration of a BZA 20 mg tablet for 8 days

Treatment C (period 3): Single dose of a CE 0.625 mg tablet plus a BZA 20 mg tablet for the first day of this period and 1 BZA 20 mg tablet alone for the next 2 days.

On Day 1 of period 1, each subject received a single oral dose of a CE 0.625 mg tablet. On Day 1 of period 2 through Day 3 of period 3, each subject received a BZA 20 mg tablet once daily. On Day 1 of period 3, single oral doses of a CE 0.625 mg tablet and a BZA 20 mg tablet were co-administered.

After a single dose administration of CE, estrogen exposure as measured by unconjugated estrone, baseline-adjusted unconjugated estrone, total estrone, baseline-adjusted estrone,

unconjugated equilin, and total equilin was not significantly affected by multiple doses of BZA suggesting that BZA does not affect CE BA.

The following table summarizes the PK parameters of Unconjugated Estrone following a single oral CE 0.625 mg tablet (Period 1) and CE 0.625 mg tablet + BZA 20 mg tablet (Period 3).

Treatment		C_{max} (pg/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_T (pg•h/mL)	AUC (pg•h/mL)
Period 1	Mean±SD	77.0±32.4	7.6±2.3	47.4±17.0	2731±1208	4609±3390
CE	%CV	42.0	30.5	35.9	44.2	73.6
	N	26	26	26	26	26
	Geometric Mean	71.7	7.3	44.7	2538	4012
	(Range)	(38.7-164)	(4.5-12.0)	(21.7-102)	(1256-7110)	(2027-19529)
Period 3	Mean±SD	86.0±36.9	8.0±2.5	44.8±16.8	2961±1357	4638±2905
CE + BZA	%CV	42.9	31.7	37.4	45.8	62.6
	N	26	26	26	26	26
	Geometric Mean	79.5	7.6	42.3	2743	4118
	(Range)	(42.5-167)	(4.5-12.0)	(24.5-94.7)	(1545-7772)	(2352-16616)
p-Values of Fixed-Effects From Mixed-Effects Model of Log-Transformed PK Parameters						
Source of Variation						
Treatment		0.038	0.573	0.186	0.019	0.359
Statistical Power (%)		99.5	75.4	-	100.0	100.0
Geometric Least Squares Means (GLS) Ratio and Confidence Intervals (CIs)[a]						
GLS Means		111	105	-	108	103
Ratio		102-120	91-120	-	103-114	98-108
90% CL						

The following table summarizes the PK parameters of Baseline-Adjusted Unconjugated Estrone following a single oral CE 0.625 mg tablet (Period 1) and CE 0.625 mg tablet + BZA 20 mg tablet (Period 3).

Treatment		C_{max} (pg/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_T (pg•h/mL)	AUC (pg•h/mL)
CE 0.625 mg	Mean±SD	57.4±28.6	7.6±2.3	15.3±7.3	1315±687	1487±855
tablet	%CV	49.8	30.5	47.9	52.3	57.5
	N	26	26	26	26	26
	Geometric Mean	51.7	7.3	13.8	1151	1282
	(Range)	(21.6-145)	(4.5-12.0)	(4.1-37.2)	(341-2752)	(377-4067)
CE 0.625 mg	Mean±SD	66.4±33.7	8.0±2.5	15.5±6.0	1533±786	1663±822
tablet with BZA	%CV	50.7	31.7	38.8	51.3	49.4
20 mg tablet	N	26	26	26	26	26
	Geometric Mean	59.4	7.6	14.2	1360	1492
	(Range)	(21.1-147)	(4.5-12.0)	(3.9-27.6)	(526-3281)	(536-3694)
p-Values of Fixed-Effects From Mixed-Effects Model of Log-Transformed PK Parameters						
Source of Variation						
Treatment		0.049	0.573	0.577	0.020	0.044
Statistical Power (%)		88.8	75.4	-	89.2	85.2
Geometric Least Squares Means (GLS) Ratio and Confidence Intervals (CIs)[a]						
GLS Means Ratio		115	105	-	118	116
90% CL		102-129	91-120	-	105-132	103-131

The following table summarizes the PK parameters of Unconjugated Equilin following a single oral CE 0.625 mg tablet (Period 1) and CE 0.625 mg tablet + BZA 20 mg tablet (Period 3).

Treatment		C_{max} (pg/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_T (pg•h/mL)	AUC (pg•h/mL)
Period 1	Mean±SD	33.3±14.9	6.6±2.6	16.9±9.6	489±287	795±323
CE	%CV	44.8	38.5	57.0	58.6	40.7
	N	26	26	24	26	24
	Geometric Mean	30.4	6.2	15.1	403	722
	(Range)	(14.7-68.5)	(4.5-12.0)	(6.0-53.7)	(97-1206)	(222-1401)
Period 3	Mean±SD	39.6±19.2	6.6±2.4	17.9±15.1	578±339	901±410
CE+ BZA	%CV	48.5	35.7	84.3	58.6	45.5
	N	26	26	26	26	26
	Geometric Mean	35.5	6.3	14.8	478	808
	(Range)	(14.5-80.2)	(4.5-12.0)	(6.1-83.2)	(124-1328)	(298-1993)
p-Values of Fixed-Effects From Mixed-Effects Model of Log-Transformed PK Parameters						
Source of Variation						
Treatment		0.008	0.944	0.927	0.004	0.013
Statistical Power (%)		97.9	70.1	-	98.1	99.1
Geometric Least Squares Means (GLS) Ratio and Confidence Intervals (CIs)[a]						
GLS Means Ratio		117	101	-	119	114
90% CL		107-128	87-117	-	108-130	105-124

The following table summarizes the PK parameters of Total Estrone following a single oral CE 0.625 mg tablet (Period 1) and CE 0.625 mg tablet + BZA 20 mg tablet (Period 3).

Treatment		C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Period 1	Mean±SD	2.53±0.77	6.5±2.3	28.9±9.2	47.5±16.0	56.8±21.6
CE	%CV	30.5	35.2	31.8	33.6	38.0
	N	26	26	26	26	26
	Geometric Mean	2.41	6.1	27.6	45.0	53.3
	(Range)	(1.01-3.92)	(4.5-12.0)	(14.3-54.1)	(19.9-84.9)	(25.5-117)
Period 3	Mean±SD	2.45±0.94	7.0±2.0	28.4±10.5	49.9±20.1	60.1±27.3
CE+BZA	%CV	38.3	28.1	36.9	40.2	45.5
	N	26	26	26	26	26
	Geometric Mean	2.29	6.7	26.7	46.4	55.3
	(Range)	(1.10-5.02)	(4.5-9.0)	(14.8-53.4)	(25.1-102)	(30.3-139)
p-Values of Fixed-Effects From Mixed-Effects Model of Log-Transformed PK Parameters						
Source of Variation						
Treatment		0.424	0.280	0.356	0.338	0.308
Statistical Power (%)		95.6	66.2	-	100.0	100.0
Geometric Least Squares Means (GLS) Ratio and Confidence Intervals (CIs)[a]						
GLS Means Ratio		95	110	-	103	104
90% CL		86-105	95-129	-	98-109	98-110

The following table summarizes the PK parameters of Baseline-Adjusted Total Estrone following a single oral CE 0.625 mg tablet (Period 1) and CE 0.625 mg tablet + BZA 20 mg tablet (Period 3).

Treatment		C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Period 1	Mean±SD	2.39±0.74	6.5±2.3	14.9±5.1	37.0±13.1	38.6±13.9
CE	%CV	31.2	35.2	34.1	35.5	36.0
	N	26	26	26	26	26
	Geometric Mean	2.26	6.1	13.9	34.6	36.0
	(Range)	(0.93-3.71)	(4.5-12.0)	(5.5-24.4)	(15.3-69.3)	(16.4-74.3)
A single CE 0.625 mg tablet in combination with a BZA 20 mg tablet CE+BZA	Mean±SD	2.30±0.92	7.0±2.0	14.2±4.6	39.1±16.5	40.9±17.8
	%CV	40.1	28.1	32.2	42.4	43.5
	N	26	26	26	26	26
	Geometric Mean	2.14	6.7	13.3	35.8	37.4
	(Range)	(1.01-4.86)	(4.5-9.0)	(3.6-26.3)	(11.8-80.2)	(11.9-88.7)
p-Values of Fixed-Effects From Mixed-Effects Model of Log-Transformed PK Parameters						
Source of Variation						
Treatment		0.390	0.280	0.314	0.358	0.357
Statistical Power (%)		93.8	66.2	-	100.0	100.0
Geometric Least Squares Means (GLS) Ratio and Confidence Intervals (CIs)[a]						
GLS Means Ratio		95	110	-	104	104
90% CL		85-105	95-129	-	97-110	97-111

The following table summarizes the PK parameters of Total Equilin following a single oral CE 0.625 mg tablet (Period 1) and CE 0.625 mg tablet + BZA 20 mg tablet (Period 3).

Treatment		C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Period 1	Mean±SD	1.55±0.52	5.4±2.0	12.1±2.9	22.7±7.8	24.1±7.8
CE	%CV	33.3	38.1	23.9	34.4	32.6
	N	26	26	26	26	26
	Geometric Mean	1.46	5.1	11.8	21.4	22.9
	(Range)	(0.58-2.69)	(3.0-12.0)	(7.6-19.4)	(8.4-39.4)	(10.5-41.1)
Period 3	Mean±SD	1.64±0.57	6.0±1.7	12.4±2.9	23.7±9.4	25.1±9.6
CE+BZA	%CV	34.5	29.2	23.3	39.9	38.1
	N	26	26	26	26	26
	Geometric Mean	1.55	5.8	12.1	22.0	23.5
	(Range)	(0.74-2.73)	(4.5-9.0)	(7.7-18.8)	(10.4-45.0)	(11.0-46.8)
p-Values of Fixed-Effects From Mixed-Effects Model of Log-Transformed PK Parameters						
Source of Variation						
Treatment		0.430	0.127	0.217	0.326	0.331
Statistical Power (%)		87.0	77.4	-	100.0	100.0
Geometric Least Squares Means (GLS) Ratio and Confidence Intervals (CI)[a]						
GLS Means Ratio		106	113	-	103	103
90% CL		94-119	99-130	-	98-108	98-107

The following table summarizes the bioequivalence comparison for CE + BZA versus CE alone.

Analyte	Comparison[a]	
	C_{max}	AUC
Unconjugated Estrone	102-120	98-108
Unconjugated Estrone Adjusted for Baseline	102-129	103-131
Unconjugated Equilin	107-128	105-124
Total Estrone	86-105	98-110
Total Estrone Adjusted for Baseline	85-105	97-111
Total Equilin	94-119	98-107

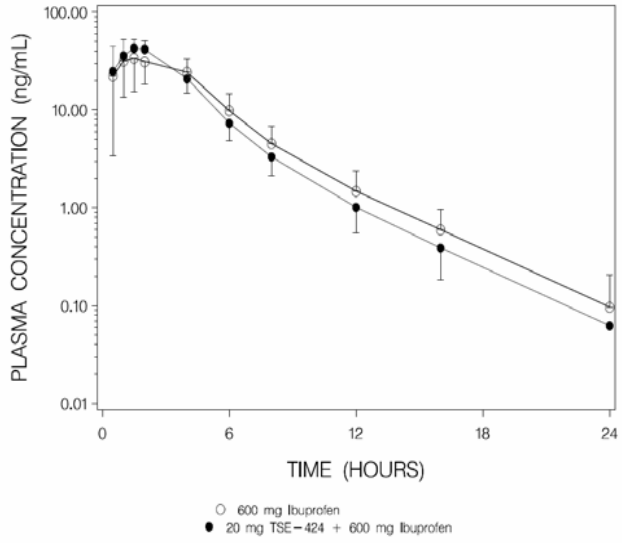
Abbreviations: AUC = total area under the concentration-time curve; C_{max} = peak concentration.
a. CE plus BZA (Test) vs. CE alone (reference).

Effect of BZA on Ibuprofen PK

Potential effects of single dose BZA 20 mg capsule on a single dose of ibuprofen 600 mg was studied in an open-label, randomized, single-dose, 3-way, crossover study in 12 healthy postmenopausal women ((b) (4) Study 106-SP (b) (4) . Each subject fasted for 10 hrs and received the following 3 treatments in 3 periods with at least 14 days washout period between treatments:

- a 600 mg ibuprofen tablet
- a 20 mg BZA capsule
- a 600 mg ibuprofen tablet + a 20 mg BZA capsule

Ibuprofen AUC and Cmax were not affected by a single dose of 20 mg BZA capsule. The following figure presents the mean plasma ibuprofen concentration-time profiles following a single BZA 20 mg capsule alone and a single dose of ibuprofen 600 mg tablet + a single BZA 20 mg capsule ((b) (4) Study 106-SP, (b) (4) .



The following table summarizes the PK parameters of ibuprofen following a single ibuprofen 600 mg tablet alone and a single dose of ibuprofen 600 mg tablet + single BZA 20 mg capsule ([(b) (4)] Study 106-SP).

Treatment	C_{max} (ng/mL)	C_{max} GLSMR	90% CI C_{max} GLSMR	AUC (ng.h/mL)	AUC GLSMR	90% CI AUC GLSMR
600 mg ibuprofen (reference)	45			168		
600 mg ibuprofen + BZD	48	106	92 - 122	168	100	94 - 106

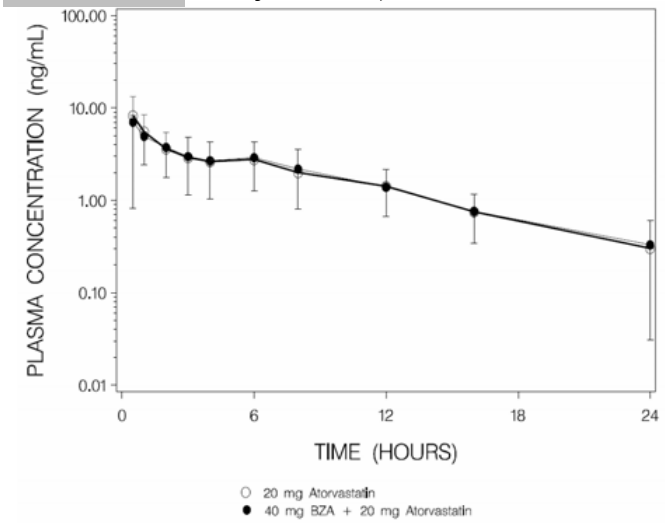
Effect of Multiple Dose BZA on Single Dose Atorvastatin PK

In a non-randomized, open-label, sequential study under fasting conditions, the applicant evaluated effect of multiple 40 mg doses of BZA on atorvastatin PK following a single 20 mg oral dose atorvastatin (Study 126-EU). Each subject received a single 20 mg atorvastatin dose alone on Day 1 and on Day 12 with 40 mg BZA. On Days 4 - 12, each subject received 9 consecutive daily 40 mg BZA doses. On Days 1, 11, and 12 (PK samples collection), subjects took the treatment drugs after a 10-hr fast.

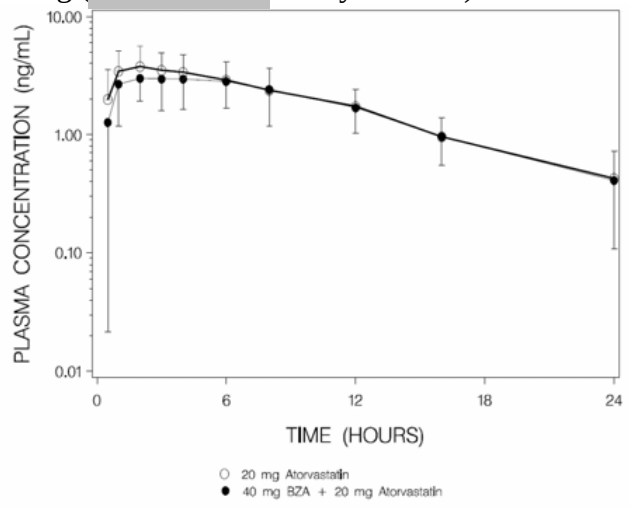
Atorvastatin Cmax was decreased by 14% following multiple daily oral doses of 40 mg BZA and a single dose of atorvastatin, compared to a single dose of atorvastatin alone. AUC was not changed.

2-OH atorvastatin Cmax and AUC were decreased by 18% and 8%, respectively, following multiple daily oral doses of 40 mg BZA and a single dose of atorvastatin, compared to a single dose of atorvastatin alone.

The following figure presents the mean plasma atorvastatin concentration-time profiles following a single dose of atorvastatin 20 mg alone and a single dose of atorvastatin 20 mg + multiple doses of BZA 40 mg ([(b) (4)] Study 126-EU).



The following figure presents the mean plasma 2-OH atorvastatin concentration-time profiles following a single dose of atorvastatin 20 mg alone and a single dose of atorvastatin 20 mg + multiple doses of BZA 40 mg ((b) (4) Study 126-EU).



The following table summarizes the PK parameters of atorvastatin following a single dose of atorvastatin 20 mg alone and a single dose of atorvastatin 20 mg + multiple doses of BZA 40 mg ((b) (4) Study 126-EU).

Treatment	C_{max} (ng/mL)	C_{max} GLSMR	90% CI C_{max} GLSMR	AUC (ng.h/mL)	AUC GLSMR	90% CI AUC GLSMR
20 mg atorvastatin (reference)	7.8			40		
20 mg atorvastatin + BZD	6.7	86	78 - 96	41	101	95 - 106

The following table summarizes the PK parameters of 2-OH atorvastatin following multiple doses of BZA 40 mg and a single dose of atorvastatin 20 mg + multiple doses of BZA 40 mg ((b) (4) Study 126-EU).

Treatment	C_{max} (ng/mL)	C_{max} GLSMR	90% CI C_{max} GLSMR	AUC_t (ng.h/mL)	AUC_t GLSMR	90% CI AUC_t GLSMR
20 mg atorvastatin (reference)	4.0			39		
20 mg atorvastatin + BZD	3.2	82	75 - 90	36.2	92	86 - 99

2.4A. Overview of Clinical Trials:

This section of the review gives a brief overview of the submitted clinical trials from the clinical pharmacology perspective (e.g., dose findings, dose-response, and formulation issues). However, for detail information related to the study design and interpretation of the clinical and the statistical/clinical significance of the safety and efficacy data, refer to the Medical Officer's and the biostatistics reviews.

Phase II Study (Dose Finding for VMS):
Study 3068A1-203-EU was a multicenter, double-blind, randomized, placebo- and active-controlled, dose-finding study of 84 days duration conducted in 408 generally healthy non-hysterectomized postmenopausal women. The doses used for the combination were 5 mg, 10 mg and 20 mg for BZA tablets and 0.3 mg and 0.625 mg for CE tablets (BZA and CE are administered as separate tablets). The results of Study 203 demonstrated that:

- 20 mg of BZA was the lowest studied dose that provided acceptable endometrial protection when administered in separate tablets with CE 0.3 mg or CE 0.625 mg.
- BZA 20 mg plus CE 0.625 mg demonstrated a significant reduction in frequency (number) and severity of VMS (hot flushes).
- BZA 20 mg plus CE 0.3 mg was not effective for the reduction in the severity of hot flushes.

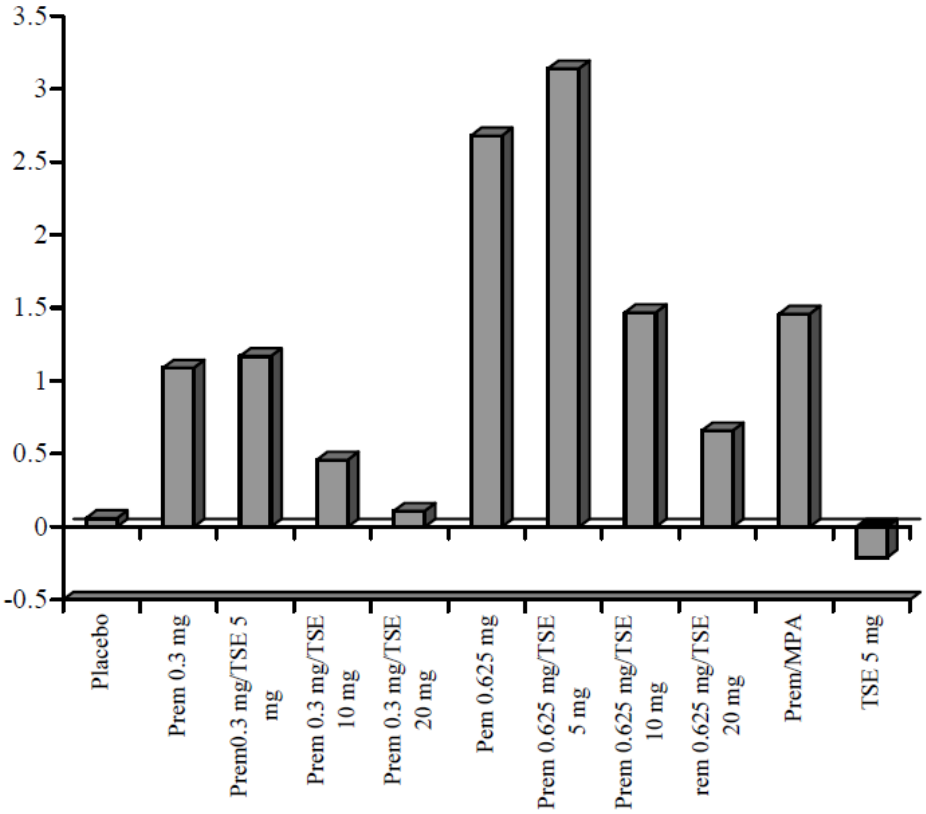
These results provided evidence that CE dose strengths higher than 0.3 mg would be required when combined with BZA 20 mg for the treatment of VMS.

Study 203:

Base on this study and other studies, BZA efficacy is dose dependent with a narrow range between 5 mg to 20 mg as highlighted below (**Figure 2.4A-1 and Table 2.4A-1**):

- Doses of 5 mg and 10 mg of BZA administered with 0.3 mg and 0.625 mg of CE were not deemed to provide high endometrial protection (i.e., based on endometrial thickness and endometrial histology data).
- However, BZA 20 mg/0.3 or 0.625 mg CE provided some endometrial protection.
- 20 mg of BZA was the lowest acceptable tested with CE 0.3 mg or CE 0.625 mg that provided endometrial protection.
- Similarly, BZA 20 mg/0.3 mg CE was **not effective** for the reduction in the severity of hot flushes. However, BZA 20 mg/CE 0.625 mg demonstrated a significant reduction in frequency (number) and severity of VMS symptoms (hot flushes).

Figure 2.4A-1: Mean Changes (mm) From Baseline in Endometrial Thickness (Local Site Evaluation) (TSE=BZA) (Study 203)



Note: TSE = tissue selective estrogen; Prem = Premarin; Prem/MPA = Premarin 0.625 mg/MPA (medroxy progesterone acetate) 2.5 mg.

Table 2.4A-1:Transvaginal Ultrasonography - Endometrial Thickness (mm) ITT Population -Analysis of Covariance (Study 203)

Visit	Treatment	N	Adjusted Mean	Standard Error	95% CI
Day 84	Placebo	27	2.95	0.38	(2.20, 3.69)
	Premarin 0.3 mg	28	3.92	0.37	(3.20, 4.65)
	TSE-424 5 mg/Premarin 0.3 mg	28	3.95	0.38	(3.21, 4.70)
	TSE-424 10 mg/Premarin 0.3 mg	29	3.27	0.37	(2.55, 3.99)
	TSE-424 20 mg/Premarin 0.3 mg	31	2.94	0.35	(2.26, 3.63)
	Premarin 0.625 mg	28	5.50	0.37	(4.77, 6.22)
	TSE-424 5 mg/Premarin 0.625 mg	28	5.99	0.37	(5.27, 6.72)
	TSE-424 10 mg/Premarin 0.625 mg	31	4.33	0.35	(3.64, 5.02)
	TSE-424 20 mg/Premarin 0.625 mg	22	3.54	0.42	(2.72, 4.37)
	Premarin 0.625 mg/MPA 2.5 mg	27	4.28	0.37	(3.55, 5.02)
	TSE-424 5 mg	29	2.64	0.37	(1.92, 3.36)

Note: CI = confidence interval; MPA = medroxy progesterone acetate; ITT = intent-to-treat. Analysis of covariance is adjusted for baseline, treatment, pooled center, and previous hormone replacement therapy.

Conclusions (Study 203):

Based on this, it can be concluded that BZA efficacy is highly dose sensitive. Any small changes in dose may results in lack of efficacy and/or endometrial protection. Therefore, any factors affecting the systemic exposure of BZA plays critical role in the therapeutic optimization.

Overview of Phase III Trials (Safety and efficacy):

As stated earlier the sponsor conducted 5 clinical safety and efficacy trials using formulations A, B, and C. These studies are summarized below:

Study 303 (Formulation A) was the first trial conducted in the BZA/CE Phase 3 clinical development program using formulation A. This was multicenter, double-blind, randomized, outpatient, 8-parallel-group, placebo- and active-controlled, dose-ranging study evaluating endometrial safety and the efficacy of BZA/CE for treatment of VMS, symptoms of VVA, and effect on BMD.

The doses of BZA/CE selected were 10 mg, 20 mg, and 40 mg of BZA formulated in a single tablet (formulation A) with either 0.45 mg or 0.625 mg of CE, resulting in 6 possible doses of BZA/CE.

Based on the data from Study 203 the sponsor selected a CE dose of 0.45 mg in Phase III study to treat moderate to severe VMS and prevention of osteoporosis. Therefore, doses of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were selected for evaluation in Study 303. Even though the BZA 10 mg dose strength when combined with CE 0.3 mg or 0.625 mg did not prevent estrogenic endometrial stimulation in Study 203, BZA 10 mg combined with 0.45 mg or 0.625 mg of CE was included in Study 303 to further characterize its effects on the endometrium.

Reference ID: 3319890

In addition, the BZA 40 mg dose, in combination with 0.45 mg or 0.625 mg of CE, was added to fully characterize the dose response for endometrial protection.

The 1-year interim results from Study 303 demonstrated that BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg have a low (<1%) incidence of endometrial hyperplasia, while reducing the frequency (number) and severity of hot flushes, improving symptoms of VVA, and preventing bone loss. Therefore, BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were selected for further evaluation in other Phase 3 studies (Studies 304, 305, 306 and 3307).

The Year 2 data from Study 303 confirmed that 20 mg is the lowest effective studied dose of BZA, combined with either 0.45 mg or 0.625 mg of CE, that provides endometrial protection (demonstrating a hyperplasia rate of <1%) as assessed by endometrial histology.

Study 304 (Formulations B and C) was a Phase 3, outpatient, multicenter, double-blind, randomized, placebo- and active-controlled clinical study evaluating the endometrial safety and efficacy of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg on BMD compared with placebo. It should be noted that all subjects started out with Formulation B then after few months switched to Formulation C (see Medical Officer's review for detail).

While Study 304 was being conducted, results of BZA/CE BE testing revealed that the BA of the BZA component in 1 of the BZA/CE formulations used (BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg, Formulation C) was not BE to Formulation A. From the BE study the BZA Cmax and AUC of Formulation C was found to be approximately 16-36% lower than that of the formulation used in Study 303 (Formulation A). Therefore, Study 304 data are considered to provide **supportive evidence** for endometrial protection and efficacy of BZA/CE for prevention of osteoporosis. For further details on the differences in formulation see Biopharmaceutics Sections 2.5 and 4.2.

Study 305 (Formulation B) was a Phase 3, multicenter, double-blind, randomized, outpatient, 3-parallel-group placebo-controlled study designed to demonstrate the efficacy of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg for the treatment of moderate to severe VMS.

Study 306 (Formulation B) was a Phase 3, multicenter, double-blind, randomized, outpatient, 4-parallel-group placebo- and active-controlled study designed specifically to assess the efficacy of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg compared with placebo and BZA 20 mg for the treatment of moderate to severe VVA. These studies (305 and 306) were of 12 weeks duration.

Study 3307 (Formulation A) was designed as the second confirmatory study (replacing Study 304 due to formulation issues) to support the endometrial safety and efficacy of BZA/CE for prevention of osteoporosis (effect on BMD). Subjects in Study 3307 received the same formulation as subjects in Study 303 (Formulation A).

Study 3307 was a Phase 3, outpatient, multicenter, double-blind, randomized, placebo- and active-controlled 5-parallel-group study designed to assess endometrial protection (incidence of endometrial hyperplasia) and efficacy for prevention of postmenopausal osteoporosis in subjects who received 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, or placebo.

Based on the above, study 3307 was conducted as a repeat of study 304 using Formulation A and/or supportive to study 304 due to formulation differences between Formulation A and C. It should be noted that Formulation A used in Study 3307 and 303 is BE to Formulation B used in the initial part of Study 304 and to the Commercial Formulation (CF) (see Biopharmaceutics Section, 2.5 and 4.2).

Below is the synopsis of the main conclusions of selected clinical trials. However, for detail analysis and discussion please see the Medical Officer's review and also the bio-statistical review.

Study 303 (Dose-Ranging):

This is a dose ranging trial for BZA/CE for endometrial protection as measured by incidence of endometrial hyperplasia and to evaluate the effect on prevention of osteoporosis (Bone Mineral Density, BMD) after 24 months of treatment. The doses of BZA/CE selected for the initial trial in the BZA/CE were 10 mg, 20 mg, and 40 mg of BZA combined into a single tablet with either 0.45 mg or 0.625 mg of CE.

The year 2 data from study 303 are shown in **Table 2.4A-3** for BZA endometrial protection and in **Figure 2.4A-1** and **Figure 2.4A-2** for efficacy in preventing osteoporosis

Both BZA 20 mg/CE 0.625 mg and BZA 20 mg/CE 0.45 mg were effective in endometrial protection. The incidence of hyperplasia was less than 1% after 24 months of treatment

Table 2.4A-3: Incidence of Endometrial Hyperplasia at Month 6 and Month 24 (Efficacy Evaluable Population)

Time Point Treatment Group	N	n	Incidence of Hyperplasia (%)	1-sided 95% CI
6 MONTHS				
CE 0.45 mg with:				
40 mg BZA	345	0	0.00	(0.00 – 0.86)
20 mg BZA	366	0	0.00	(0.00 – 0.82)
10 mg BZA	354	0	0.00	(0.00 – 0.84)
CE 0.625 mg with:				
40 mg BZA	354	0	0.00	(0.00 – 0.84)
20 mg BZA	352	1	0.28	(0.01 – 1.34)
10 mg BZA	371	6	1.62	(0.71 – 3.17)
Raloxifene 60 mg	344	0	0.00	(0.00 – 0.87)
Placebo	348	0	0.00	(0.00 – 0.86)
24 MONTHS				
CE 0.45 mg with:				
40 mg BZA	268	0	0.00	(0.00 – 1.11)
20 mg BZA	293	1	0.34	(0.02 – 1.61)
10 mg BZA	277	7	2.53	(1.19 – 4.69)
CE 0.625 mg with:				
40 mg BZA	267	0	0.00	(0.00 – 1.12)
20 mg BZA	271	2	0.74	(0.13 – 2.30)
10 mg BZA	294	21	7.14	(4.84 – 10.12)
Raloxifene 60 mg	261	0	0.00	(0.00 – 1.14)
Placebo	259	0	0.00	(0.00 – 1.15)

n = number of subjects with hyperplasia at any time during the study up to and including the given time point.
N = number of subjects with biopsies available at the time point plus all subjects with hyperplasia prior to the time point.

Figure 2.4A-1: Percent Change from Baseline (SE) to Month 24 in BMD of Lumbar Spine (Study 303)

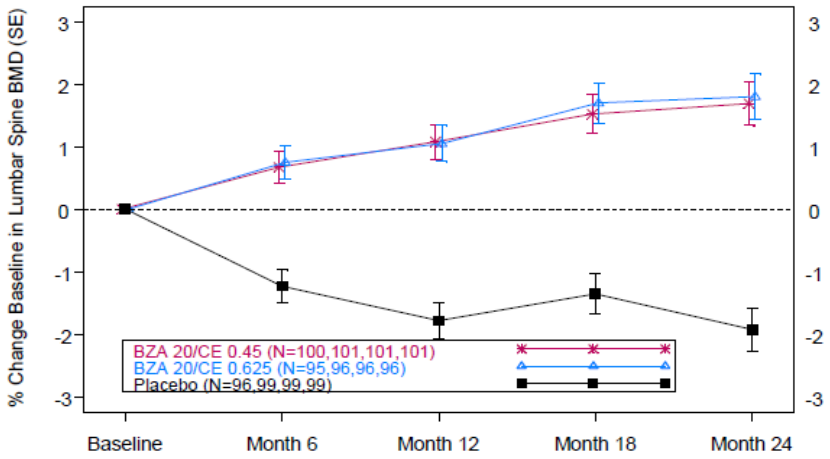
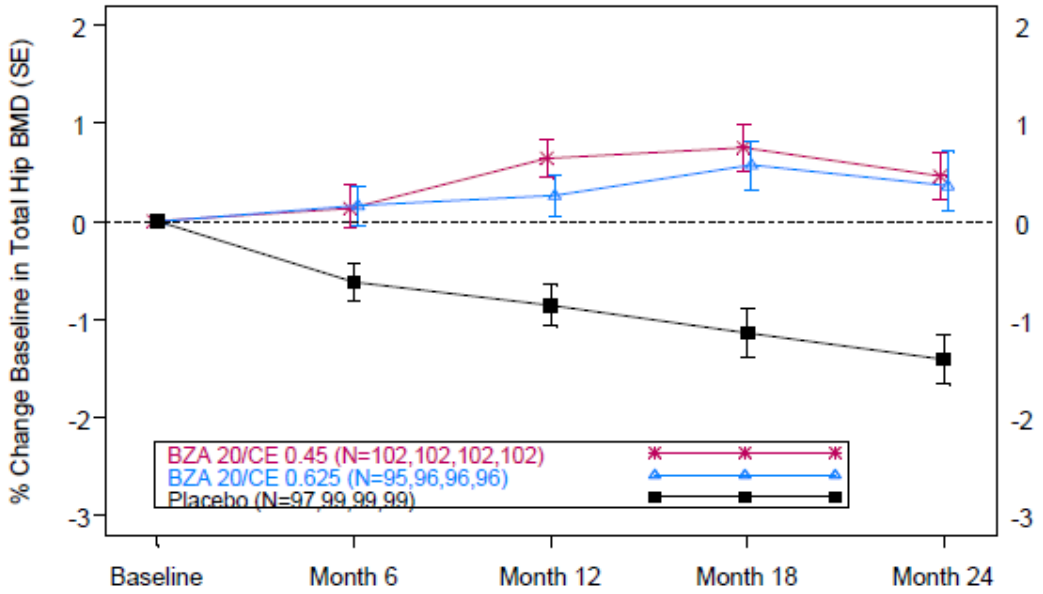


Figure 2.4A-2: Percent Change from Baseline (SE) to Month 24 in Total Hip BMD (Study 303)



Efficacy assessment of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg therapy in the prevention of osteoporosis (as measured by changes in BMD) was based on the results at Month 12 and to lesser extent at 24 in Study 303 and at Month 12 in Study 3307. Treatment with BZA/CE demonstrated an increase in lumbar spine and total hip BMD compared with placebo after 6 months of treatment and this effect was evident up to 24 months of treatment.

Is There Dose-Response Relationship for CE in the Prevention of Osteoporosis?

As shown above, the difference in the effect on BMD between 20 mg/0.45 mg and 20 mg/0.625 mg doses is small. No additional benefit was observed with the higher dose of 20/0.625 mg over 20/0.45 mg. However, there was significant separation in both BMD and Total Hip BMD between placebo and both doses.

Reviewer's Comments:

It should be noted, that estrogenic efficacy as well as the effect on BMD was highest at 12 months of treatment in which it collapses at 24 months. Therefore, it is not known at this time what would be the efficacy beyond 24 months. In addition, there was little separation between the CE doses at 24 months.

However, for further interpretation of this data please refer to the Medical Officer's and Biostatistics reviews.

Study 3307 (Confirmatory Study):

As stated earlier, this study was a substitution for Study 304 in which the BZA exposure from formulation C was lower than that of formulation A that was used in Study 303. Therefore, study 304 will remain supportive to the clinical program. The primary objective of study 3307 is the same as that of 304 which is to assess endometrial protection (incidence of endometrial hyperplasia) and efficacy for prevention of postmenopausal osteoporosis. The treatment regimens and the formulations used in this study are shown below:

Regimen	Capsule
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
5	Placebo

BZA=bazedoxifene; CE=conjugated estrogens; MPA=medroxyprogesterone acetate.

Drug Product/Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA 20 mg/CE 0.45 mg	Capsule[a]	0931530D	2008B0212 2009B0016
BZA 20 mg/CE 0.625 mg	Capsule[a]	0931534D	2008B0197 2009B0009 2009B0149
BZA 20 mg	Capsule[a]	0932219D	2008B0168
CE 0.45 mg/MPA 1.5 mg	Capsule[a]	0932770D	2008B0236 2009B0148
Placebo	Capsule	0931539D	2008B0176

a. Tablets over-encapsulated for blinding purposes.

A total of 1886 subjects were randomly assigned to the test article treatment groups; 43 randomly assigned subjects did not take the test article and thus are not included in any analyses. The remaining 1843 subjects took at least one dose of test article and are included in the safety analyses. These subjects were randomly assigned as follows:

- 445 to BZA 20mg/CE 0.45 mg
- 474 to BZA 20mg/CE 0.625 mg
- 230 to BZA 20 mg
- 220 to CE 0.45/MPA 1.5 mg
- 474 to placebo

In terms of the endometrial protective effect, all endometrial biopsies were centrally read by 2 primary pathologists. If the 2 primary pathologists disagreed with respect to the presence of hyperplasia then a third pathologist was consulted. The final diagnosis and identification of hyperplasia was based on readings from 3 pathologists and defined by two ways:

Definition 1: The outcome was determined to be hyperplasia when the 3 pathologists disagreed but at least 1 pathologist determined hyperplasia.
Definition 2: Required that a diagnosis of hyperplasia was made if at least 2 of the 3 pathologists agreed on the diagnosis.

Based on these definations, **Tables 2.4A-4 and 5** show the summary of the hyperpensia data at 12 months:

Using Definition 1, no cases of endometrial hyperplasia were observed in the BZA 20 mg or the CE 0.45 mg/MPA (medroxyprogesterone acetate) 1.5 mg treatment groups, and 1 case of endometrial hyperplasia was seen in the BZA 20mg/CE 0.45 mg treatment group, (b) (4) in the BZA 20 mg/CE 0.625 mg treatment group and 3 cases in the placebo treatment group (**Table 2.4A-4**).

The incidence rate of hyperplasia in the BZA 20 mg/CE 0.45 mg treatment group was 0.30% (1-sided 95% CL: 1.41, 2-sided 95% upper CL: 1.65) and (b) (4)) in the BZA 20 mg/CE 0.625 mg treatment group. Both BZA/CE groups had 1-sided 95% CLs of less than 4% and upper 2-sided 95% CLs of less than 2%.

Table 2.4A-4: Incidence of Endometrial Hyperplasia at Month 12 (Definition 1, Study 3307)

Treatment Group	n	Number of Subjects With Hyperplasia	Hyperplasia Rate (%)	Upper Limit 95% CI (1-sided)	Upper Limit 95% CI (2-sided)
BZA 20 mg/CE 0.45 mg	335	1	0.30	1.41	1.65
(b) (4)					
BZA 20 mg	169	0	0.00	1.76	2.16
CE 0.45 mg/MPA 1.5 mg	149	0	0.00	1.99	2.45
Placebo	354	3	0.85	2.18	2.46

For definition 2 (**Table 2.4A-5**), no cases of endometrial hyperplasia were observed in the BZA 20 mg or the CE 0.45 mg/MPA (medroxyprogesterone acetate) 1.5 mg treatment groups, and 1 case of endometrial hyperplasia was seen in each of the BZA 20mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg and the placebo treatment groups.

The incidence rate of hyperplasia in the BZA 20 mg/CE 0.45 mg treatment group was 0.30% (1-sided 95% upper CL [Confidence Limit]: 1.41, 2-sided upper 95% CL: 1.65) and was (b) (4) in the BZA 20 mg/CE 0.625 mg treatment group. Both BZA/CE treatment groups had an incidence rate of endometrial hyperplasia of less than 1%. Both BZA/CE treatment groups were associated with an upper 1-sided 95% CL of less than 4% and upper 2-sided 95% CLs of less than 2%.

Table 2.4A-5: Incidence of Endometrial Hyperplasia at Month 12 (Definition 2, Study 3307)

Treatment Group	n	Number of Subjects With Hyperplasia	Hyperplasia Rate (%)	Upper Limit 95% CI (1-sided)	Upper Limit 95% CI (2-sided)
BZA 20 mg/CE 0.45 mg	335	1	0.30	1.41	1.65
[redacted]					(b) (4)
BZA 20 mg	169	0	0.00	1.76	2.16
CE 0.45 mg/MPA 1.5 mg	149	0	0.00	1.99	2.45
Placebo	354	1	0.28	1.33	1.56

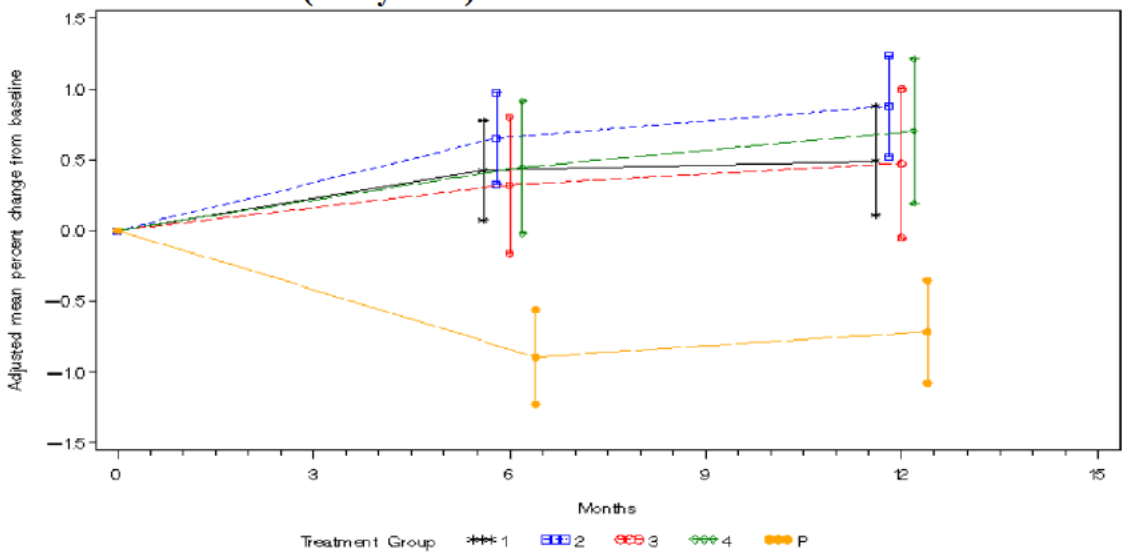
Based on this study, there was separation in the percentage of changes from baseline for BMD between active treatments and placebo (**Table 2.4A-6 and Figure 2.4A-3**).

Table 2.4A-6: Adjusted Mean Percentage Changes From Baseline in the BMD of the Total Hip at Month 6 and Month 12 (Study 3307)

			Adjusted % change		Adjusted Difference vs. Placebo		p-value			
Treatment	Time slot	N[a]	Mean	SE	Mean	95% CI	Within group	vs. placebo	vs. BZA 20 mg	vs. CE 0.45 mg/ MPA 1.5 mg
BZA 20 mg/ CE 0.45 mg	Month 6	117	0.43	0.18	1.32	(0.901, 1.742)	0.017	<0.001	0.706	0.920
	Month 12	119	0.50	0.20	1.21	(0.756, 1.671)	0.011	<0.001	0.936	0.478
[redacted]										(b) (4)
BZA 20 mg	Month 6	55	0.32	0.25	1.22	(0.685, 1.750)	0.190	<0.001		0.680
	Month 12	56	0.47	0.27	1.19	(0.610, 1.769)	0.078	<0.001		0.499
CE 0.45 mg/ MPA 1.5 mg	Month 6	57	0.45	0.24	1.35	(0.823, 1.875)	0.058	<0.001		
	Month 12	59	0.71	0.26	1.42	(0.854, 1.994)	0.006	<0.001		
Placebo	Month 6	134	-0.90	0.17			<0.001			
	Month 12	139	-0.72	0.18			<0.001			

a. Number of pairs.

Figure 2.4A-3: Adjusted Percent Change From Baseline in Total Hip Bone Mineral Density at Month 6 and Month 12 (Study 3307)



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

Conclusion:

Overall, the data from this study (3307) is comparable and confirmatory to those observed studies 303 (for details, please see the Medical Officer's review and the biostatistics review).

Study 304 (Endometrial Protective Effect)

This was multicenter, double-blind, randomized, placebo- and active-controlled clinical study evaluating the endometrial safety and efficacy of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg on BMD compared with placebo.

The study included an osteoporosis substudy in subjects who were ≤5 years postmenopausal. The primary objectives were to assess the effect of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg compared with placebo on the incidence of endometrial hyperplasia (endometrial protection) and the prevention of postmenopausal osteoporosis (change in lumbar spine BMD) after 1-year.

The secondary objectives of this study were to provide BMD data for descriptive comparison of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg versus an active comparator (CE 0.45 mg/MPA 1.5 mg, Prempro®). In addition, the study was to assess the effect of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg on amenorrhea (cumulative and noncumulative), and on breast pain versus placebo and an active comparator (CE 0.45 mg/MPA 1.5 mg), after 1-year of therapy.

As stated earlier, while this study being conducted, results of BZA/CE bioequivalence testing revealed that the bioavailability of the BZA component in Formulation C used in this study was approximately 18% lower than the bioavailability of the BZA component in the formulation A used in Study 303. However, considering the three BE studies (single dose and multiple doses) that were conducted; the Cmax and AUC from Formulation C were approximately 16% to 36% lower than formulation A.

Therefore, this study is considered to provide only supportive evidence for endometrial protection and efficacy of BZA/CE for prevention of osteoporosis. Thus, study 3307 was conducted with formulation A as a replacement to this study. Formulation A is bioequivalent to the final-to-be marketed (TBM) formulation (see biopharmaceutics Section 4.2).

Based on this study, at the 12 month time point, 1 case of endometrial hyperplasia was observed in the BZA 20 mg/CE 0.45 mg treatment group resulting in an incidence of hyperplasia of 0.38%, and (b) (4) in the BZA 20 mg/CE 0.625 mg treatment group (**Table 2.4A-7**).

Table 2.4A-7: Incidence of Endometrial Hyperplasia at Month 12 Using the Alternate Definition of Hyperplasia (Study 304)

Treatment Group	n[b]	Number of Subjects With Hyperplasia[c]	Hyperplasia Rate (%)	95% CI[a] LL	UL
BZA 20 mg/CE 0.45 mg	261	1	0.38	0.02	1.80
[redacted]					(b) (4)
CE 0.45 mg/MPA 1.5 mg	119	1	0.84	0.04	3.92
Placebo	135	0	0.00	0.00	2.19

a. 1-sided.
b. Number of subjects.
c. Based on agreement of 2 pathologists.

In terms of effect on BMD, both BZA/CE treatment groups had significant increases from baseline in lumbar spine BMD at month 12 (within group, p = 0.001), and the increases were significantly different from the significant decreases from baseline observed in the placebo group (p < 0.001, **Table 2.4A-8**). In both BZA/CE groups, the increases from baseline were significantly less than those observed in the CE 0.45 mg/MPA 1.5 mg group (p < 0.001).

Table 2.4A-8: Adjusted Mean Percentage Changes From Baseline to Month 12 in the BMD of the Lumbar Spine (Study 304)

Treatment Group	N[a]	Adjusted Change Mean	SE	Adjusted Difference- Mean	95% CI	p-Value Within Group	vs CE 0.45 mg /MPA 1.5 mg	vs Placebo
BZA 20 mg/CE 0.45 mg	146	0.80	0.24	2.37	(1.56, 3.18)	0.001	< 0.001	< 0.001
[redacted]								(b) (4)
CE 0.45 mg/MPA 1.5 mg	60	2.22	0.37	3.78	(2.81, 4.76)	< 0.001	--	< 0.001
Placebo	65	-1.56	0.35	--	--	< 0.001	--	--

Ancova model: percentage change from baseline = treatment + site + baseline BMD + years since menopause.
a. Number of pairs.

Conclusions:

In this study the rate of hyperplasia was >1% (1.47%) after 12 months of treatment. This study failed to demonstrate adequate endometrial protection.

Study 305 (VMS):

This was multicenter, double-blind, randomized, 3-parallel-group placebo-controlled study designed to demonstrate the safety and efficacy of 2 doses of BZA/CE (BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg) compared with placebo for the treatment of moderate to severe VMS associated with menopause in 318 women (n=127 at 20/0.45 mg, [redacted] (b) (4) 20/0.625 mg, and n= 63 for placebo). The duration of the study was 12 weeks. Formulation B was used in this study.

Based on this study, the mean change from baseline in the average daily number of moderate and severe hot flushes at the severity of [redacted] (b) (4) at weeks 4 and 12 are significant following treatments compared to placebo (**Figures 2.4A-4 and 5 and Tables 2.4A-9 and 10**).

Reference ID: 3319890

All treatment groups were associated with a significant decrease from baseline ($p < 0.001$) in the adjusted mean daily number of moderate and severe hot flushes at all time points, reaching a 74% and a (b) (4) reduction from baseline in the BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg treatment groups, respectively, at week 12, compared with a 51% reduction in the placebo group.

Over the 12 weeks of therapy, significant differences were observed between BZA/CE and placebo in the average daily number of moderate and severe hot flushes, beginning at week 3 in the BZA 20 mg/CE 0.45 mg treatment group ($p = 0.008$) and at week 2 in the BZA 20 mg/CE 0.625 mg ($p = 0.007$) treatment group, and continued through week 12.

Both BZA/CE treatment groups had significant decreases from baseline ($p < 0.001$) in the adjusted mean daily severity (b) (4) of hot flushes at all time points.

Is There Dose-Response Relationship for CE in the Treatment of VMS?

When combined with BZA 20 mg, CE 0.625 mg appears better in reducing the average daily severity (b) (4) of hot flushes compared with CE 0.45 mg, but similar in reducing the average daily number of moderate to severe hot flushes (**Figures 2.4A-4 and Figure 5**).

Figure 2.4A-4: Average Daily Number of Moderate and Severe Hot Flushes, Week 1 Through Week 12 (Study 305)

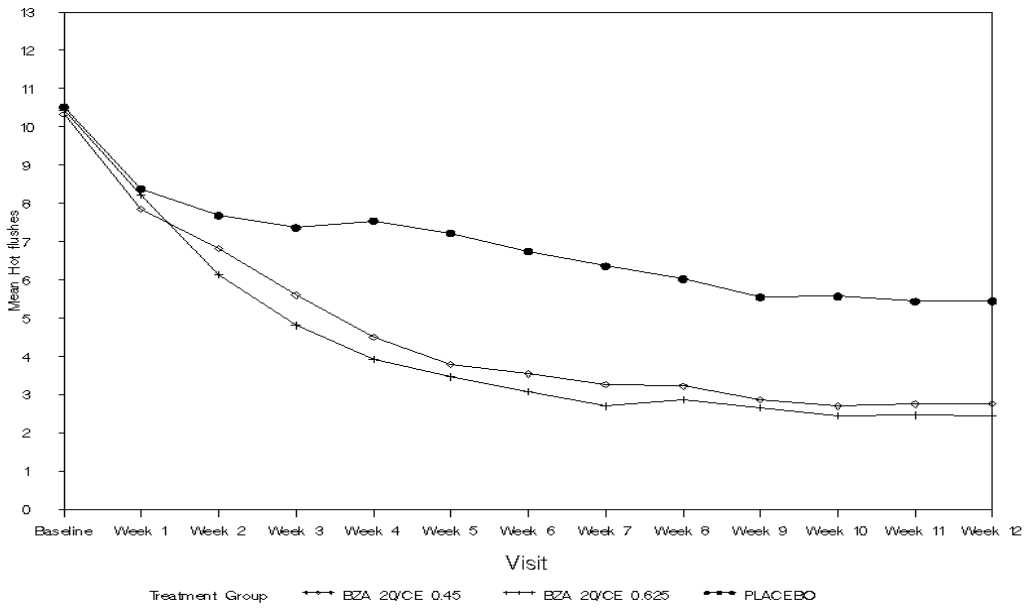
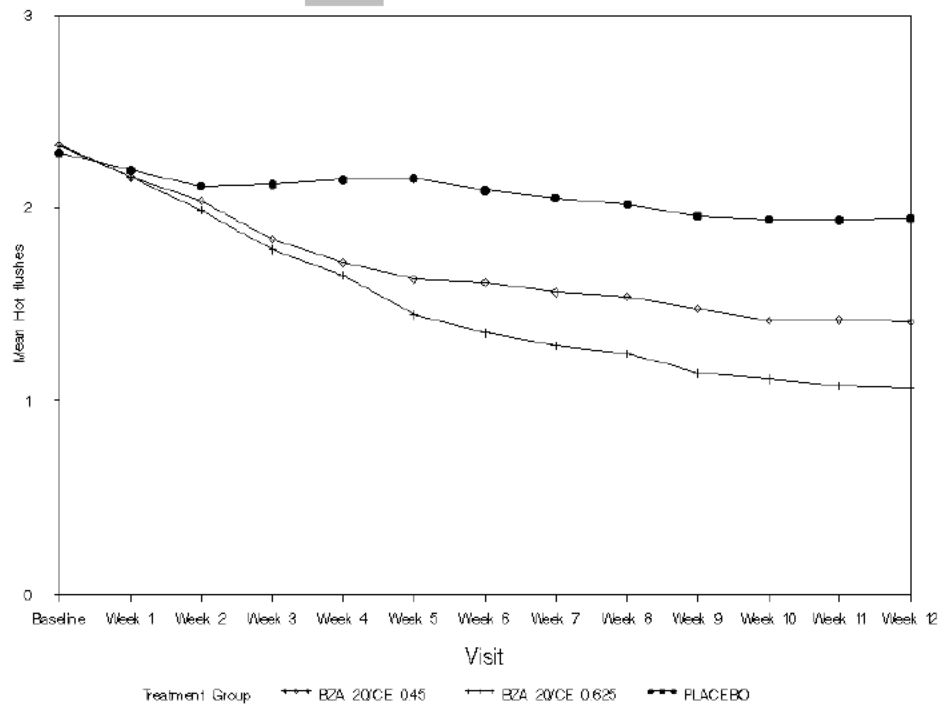


Table 2.4A-8: Mean (SE) Change From Baseline in the Average Daily Number of Moderate and Severe Hot Flushes at Week 4 and Week 12 (Study 305)

			--Adjusted Change--		
Treatment	**Time Slot**	**No. of Pairs**	**Mean**	**SE**	**p-Value vs Placebo**
LOCF					
BZA 20 mg/CE 0.45 mg	Week 4	122	-5.90	0.42	< 0.001
	Week 12	122	-7.63	0.36	< 0.001
[redacted]					(b) (4)
Placebo	Week 4	63	-2.84	0.56	--
	Week 12	63	-4.92	0.48	--
OC					
BZA 20 mg/CE 0.45 mg	Week 4	119	-5.91	0.43	< 0.001
	Week 12	109	-7.96	0.39	< 0.001
[redacted]					(b) (4)
Placebo	Week 4	61	-2.79	0.57	--
	Week 12	53	-5.22	0.54	--

Figure 5: Average Daily Severity [redacted] (b) (4) Hot Flushes, Week 1 Through Week 12 (Study 305)



Reference ID: 3319890

Table 9: Mean (SE) Change from Baseline in the Average Daily Severity (b) (4) of Hot Flushes at Week 4 and Week 12 (Study 305)

Treatment	Time Slot	No of Pairs	--Adjusted Change-- Mean	SE	p-Value vs Placebo
LOCF					
BZA 20 mg/CE 0.45 mg	Week 4	122	-0.58	0.07	< 0.001
	Week 12	122	-0.87	0.08	< 0.001
(b) (4)					
Placebo	Week 4	63	-0.09	0.09	--
	Week 12	63	-0.26	0.11	--
OC					
BZA 20 mg/CE 0.45 mg	Week 4	119	-0.58	0.07	< 0.001
	Week 12	109	-0.92	0.09	< 0.001
(b) (4)					
Placebo	Week 4	61	-0.11	0.09	--
	Week 12	53	-0.34	0.12	--

Based on this study, it can be concluded that the combination of BZA/CE provided better effect on hot flushed and the severity of hot flushes compared to the placebo. (b) (4)

However, for in depth analysis of the data and final conclusions from this study, please see the Medical Officer's and biostatistics reviews.

Study 306 (VVA):

(b) (4)

(b) (4)

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

2.4 B. Pharmacometric Analysis of Phase III Studies

SUMMARY OF FINDINGS

The proposed dosing regimen BZA 20 mg /CE0.45 mg is acceptable from the pharmacometric perspective. The BZA dose of 20 mg is the minimum effective dose among the tested doses when combined with 0.45 or 0.625 mg CE. Low BZA dose of 10 mg failed to provide adequate endometrial protection, and higher BZA dose of 40 mg caused unacceptable efficacy loss.

Except for endometrial protection and improved tolerability, BZA did not show positive contribution to the three estrogenic efficacy endpoints (VMS, VVA, and Prevention of Osteoporosis). Instead, it attenuated the desired treatment effect in a dose-dependent manner. The higher the BZA dose, the more the estrogenic efficacy loss was observed. When BZA dose was 40 mg, no significant difference was shown for VMS and VVA between BZA/CE and the placebo groups.

One prominent challenge of using BZA/CE was how to optimize BZA exposure. (b) (4) A relative small drop in BZA exposure could lead to significant increase in the rate of endometrial hyperplasia. (b) (4) (b) (4) In this regard, subjects with significantly high clearance to BZA due to intrinsic or extrinsic factors may be at risk of underexposure and more likely to develop hyperplasia. BZA did not show narrow therapeutic index for endometrial protection when combined with low CE dose of 0.45 mg (Figure 16 in Pharmacometrics Analysis).

(b) (4) (b) (4)

Key Review Questions

The purpose of this review is to address the following key questions.

Is there any evidence of dose-response relationship for BZA in endometrial protection?

Bazedoxifene demonstrated clear dose-dependent effect in endometrial protection. The rate of endometrial hyperplasia decreased with increasing bazedoxifene doses. Larger effect was observed in patients treated with lower dose of CE, suggesting that the effect of BZA was dependent on the CE dose. As shown in **Table 2.4 B-1**, in study 303, after 12 months of treatment, the 40 mg dose of BZA showed a full protection of endometrium under the studied sample size when combined with either 0.625 mg or 0.45 mg of CE. There was no endometrial hyperplasia case observed. For a reduced dose of 20 mg BZA, the complete protection was only achieved at the low dose of CE (0.45 mg), (b) (4)

[redacted] The protection was further reduced to an unacceptable level when the dose of BZA was lowered to10 mg. In terms of endometrial protection, BZA 20 mg may be considered the minimum effective dose that will produce an acceptable rate of hyperplasia when combined with 0.45 or 0.625 mg CE. This result is consistent with findings from study 203, a Phase II, dose-finding study.

Table 2.4 B-1: Incidence of Endometrial hyperplasia at Month 12 (Study 3115A1-303, Efficacy Evaluation Population)

Treatment Group[a]	N	n	Incidence of Hyperplasia (%)	CI[b]
CE 0.45 mg with:				
40 mg BZA	309	0	0.00	(0.00 – 1.19)[c]
20 mg BZA	335	0	0.00	(0.00 – 1.10)[c]
10 mg BZA	320	3	0.94	(0.26 – 2.41)
CE 0.625 mg with:				
[redacted]				
Raloxifene 60 mg	298	0	0.00	(0.00 – 1.00)
Placebo	312	0	0.00	(0.00 – 0.96)

n = number of subjects with hyperplasia at any time during the study up to and including month 12.

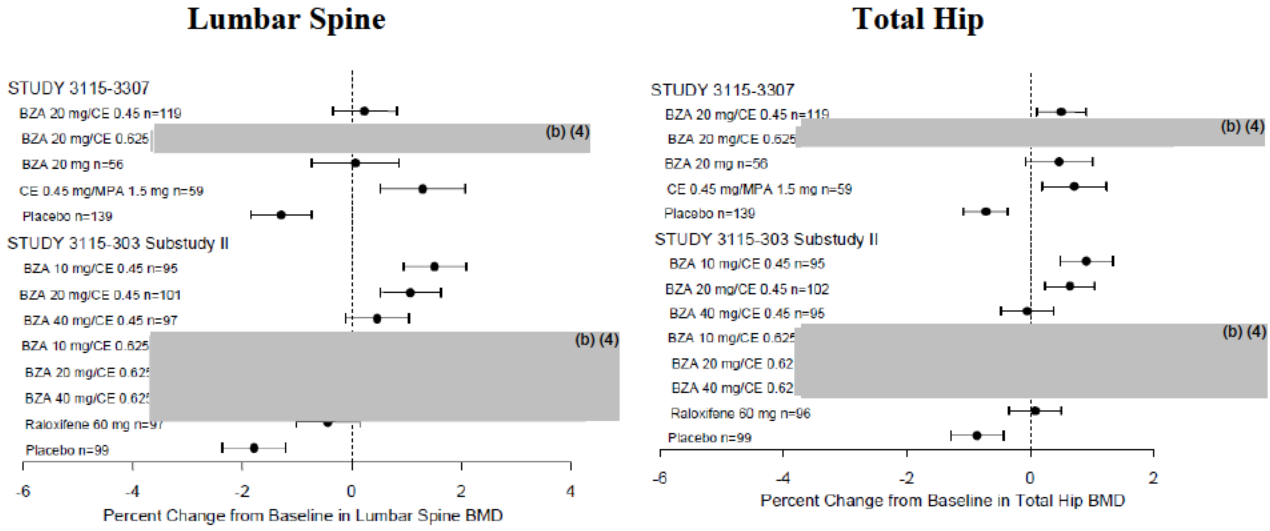
Source: Table 9-2 on page 103 of sponsor's report 3115A1-303-US/EU/BR

However, it is worth noting that study 304 did not show acceptable endometrial protection. [redacted] The rate was even higher after 24 months or using FDA's definition of hyperplasia. The lack of protection is believed by the sponsor to be due to formulation C which was found to have a 30% lower steady state BZA exposure than the formulation used in Study 303 and 3307 (Formulation A) in the population PK analysis . [redacted]

Is there any evidence of dose-response relationship for BZA in the prevention of post menopausal osteoporosis?

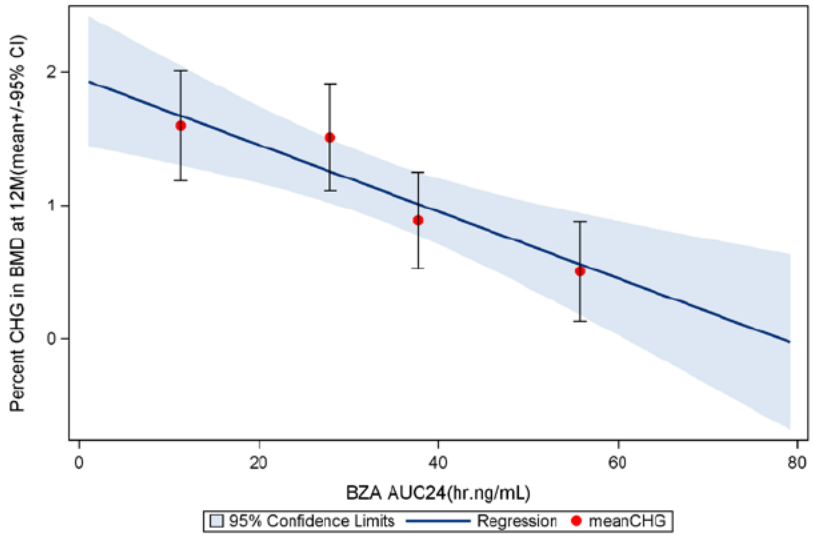
BZA did not show synergistic benefit in preventing bone loss when combined with CE. Instead, it attenuated the preventive effect of CE in postmenopausal osteoporosis. After BZA/CE treatment for 12 months, lumbar spine and total hip bone density decreased with increased bazedoxifene doses (**Figure 2.4B-1**). Despite the induced efficacy loss by BZA, the BZA/CE combination remained effective in preventing postmenopausal bone loss. The proposed dosing regimen (BZA 20 mg/ CE 0.45 mg, BZA 20 mg/CE 0.625mg) demonstrated significantly better effect than the placebo, as well as the approved drug in the same class, raloxifene (60 mg).

Figure 2.4 B-1: Percentage Change from Baseline (95% CI) to Month 12 in BMD of Lumbar Spine and Total Hip (MITT Population, LOCF)



A plot of change in spine BMD at Month 12 versus BZA exposure (population PK model-estimated AUC) in patients from study 303 and 304 confirmed the attenuating effect of BZA in preventing bone loss under BZA/CE treatment. Higher bazedoxifene exposure was associated with lower bone density (**Figure 2.4B-2**).

Figure 2.4B-2: Relationship between change in lumbar spine bone mineral density at 12 Month vs bazedoxifene exposure (study 303 and 304 combined)

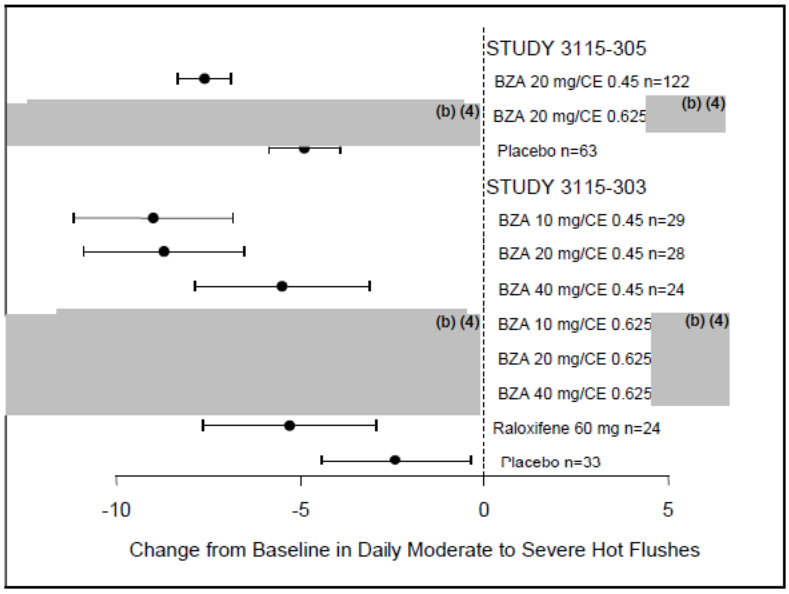


Is there any evidence of dose-response relationship for BZA in the treatment of VMS?

In study 305, the proposed BZA 20 mg/ CE 0.45 mg and BZA 20 mg/ CE 0.625 mg treatments were statistically more effective than the placebo group ($p<0.001$) and raloxifene 60 mg ($p=.032$)

in the management of hot flushes after 12 weeks. However, BZA did not show additional benefit when combined with CE. By contrast, BZA reduced CE effect in a dose-dependent manner. As shown in **Figure 2.4B-3**, in Study 303, higher dose BZA was associated with higher number of daily number of moderate and severe hot flushes. (b) (4)

Figure 2.4.B-3: Percent Change from Baseline (95% CI) in Number of Moderate of Severe Hot Flushes at Week 12: Study 305 (MITT, LOCF) and Study 303 (EE1, LOCF) (MITT, LOCF)



Source: Figure 3-1 on Page 137 of sponsor's ISE report

Is there any evidence of dose-response relationship for BZA in the treatment of VVA?

(b) (4)


(b) (4)


(b) (4)

(b) (4)

(b) (4)

However, we do not recommend BZA 20 mg /CE 0.625 mg. (b) (4)

(b) (4)

2.5 General Biopharmaceutics

Overview:

The sponsor conducted 15 biopharmaceutics studies primarily related to formulation development. The formulation development in this NDA is complex due to many changes in formulations during the product development.

The proposed TBM BZA/CE doses are 20 mg/0.45 mg and 20 mg/0.625 mg. The proposed TBM formulations consist of the commercial 0.45 mg or 0.625 mg Premarin® (CE) (b) (4) (Figure 2.5.1).

Figure 2.5.1: Scheme Representing BZA/CE and Premarin® Tablets.

(b) (4)

(b) (4)

Extensive formulation and process development, dissolution development, and biopharmaceutic studies have been conducted to develop the final proposed TBM BZA/CE drug product. These biopharmaceutics studies are part of a more extensive clinical pharmacology program for BZA/CE.

In order to understand the complexity of the biopharmaceutics program, the following terminology and acronyms are first defined:

- **PCP** Formulations = Premarin current process formulations
- **PNP** Formulations = Premarin new process formulations
- **PCP** refers to the formulation used to manufacture Premarin tablets for the US market approximately prior to 2004, which utilized [redacted]
- **PNP** refers to the formulation used to manufacture Premarin tablets for the US market after the initial approval in 2004, which utilize [redacted]
- **Formulation A** refers to the family of BZA/CE tablet formulations with a [redacted] that share a similar composition, but differ in the strength of BZA and CE. Formulation A was used in clinical Studies 3115A1-303-US/EU/BR and 3115A1-3307-WW (**Table 2.5.1.1**).
- **Formulation B** refers to the family of BZA/CE tablet formulations that introduced the [redacted] and share a similar composition, but differ in the strength of BZA and CE. Formulation B was used in clinical Studies 3115A1-305-US and 3115A1-306-WW, and in the early part of Study 3115A1-304-WW (**Table 2.5.1.1**).
- **Formulation C** refers to the BZA/CE tablet formulation that introduced [redacted] Formulation C was one of the formulations used in clinical Study 3115A1-304-WW (**Table 2.5.1.1**).
- **Formulation D** refers to the family of BZA/CE tablet formulations that share a similar composition, [redacted]. The original Formulation D was enhanced by [redacted] Formulation D was only used in Phase 1 clinical studies (**Table 2.5.1.1**).

Table 2.5.1.1: Formulations of BZA/CE Used in this NDA

Formulation	A	B	C	D (Including Proposed TBM)
Type of Study	2-year Phase 3 endometrial safety, BMD, VVA, and VMS study (3115A1-303-US/EU/BR) 1-year Phase 3 endometrial safety and osteoporosis prevention study (3115A1-3307-WW) Food Effect study (3115A1-102-US) Drug Interaction Study (3115A1-101-US) BA/BE Studies (3115A1-100-US, 3115A1-109-US, 3115A1-114-US, 3115A1-1120-US, 3115A1-1121-US, 3115A1-1117-US, 3115A1-1122-US, 3115A1-1137-US, 3115A1-1117-US	2-year Phase 3 endometrial safety and BMD study (3115A1-304-WW) 3-month Phase 3 VMS study (3115A1-305–US) 3-month Phase 3 VVA study (3115A1-306-WW) BA/BE Studies (3115A1-1117-US, 3115A1-1139-US, 3115A1-1142-US IVIVC Study (3115A1-115-US)	Phase 3 Study 3115A1-304-WW Used Formulation C for 8 months of first year and all of second year BA/BE Studies (3115A1-114-US, 3115A1-1120-US, 3115A1-1121-US, 3115A1-1117-US, Food Effect Study (3115A1-1116-US)	Proposed TBM only used in these 4 bioequivalence studies: (3115A1-1122-US, 3115A1-1139-US, 3115A1-1137-US, 3115A1-1142-US) Other studies using Formulation D: BA/BE Study (3115A1-1117-US) Multiple-Dose Study (3115A1-1138-US) BZA Polymorph Study (3115A1-1143-US)
Formulation Description	[redacted] (b) (4)			

Abbreviations: BMD = bone mineral density; BR = Brazil; CE = conjugated estrogens; EU = European Union; PCP = Premarin current process; PNP = Premarin new process; US = United States; VMS = vasomotor symptoms; VVA = vulvar-vaginal atrophy; WW = world-wide.
Source: Module 3.0 (3.2.P.2.2), Table 3

Due to the complexity of the biopharmaceutics and formulation program, an information request (IR) letter was sent to the sponsor on March 21, 2013 to provide clarification on bridging of all the formulations and to provide framework on the steps taken for each formulation changes. On April 5, 2013, the sponsor provided a response including **Figures 2.5.1.2-3** and Tables **2.5.1.2-5** to clarify the complexity of the process.

Figure 2.5.1.2 shows the comparative changes/structure between:

- Formulation A which was used in the clinical studies 3115A1-303-US/EU/BR and later in another trial (3115A1-3307-WW)
- Formulation B used in the clinical trial 304,
- Formulation C used in the later part of clinical trial 304, and
- Formulation D (commercial formulation, CF) used **only** in BA/BE studies.

Figure 2.5.1.2: Comparative Scheme of the (b) (4) Changes from First Formulation (A) to Commercial Formulation (CF or D)

Figure 2.5.1.3 shows the relationship between Formulation A, B C, and D (CF).

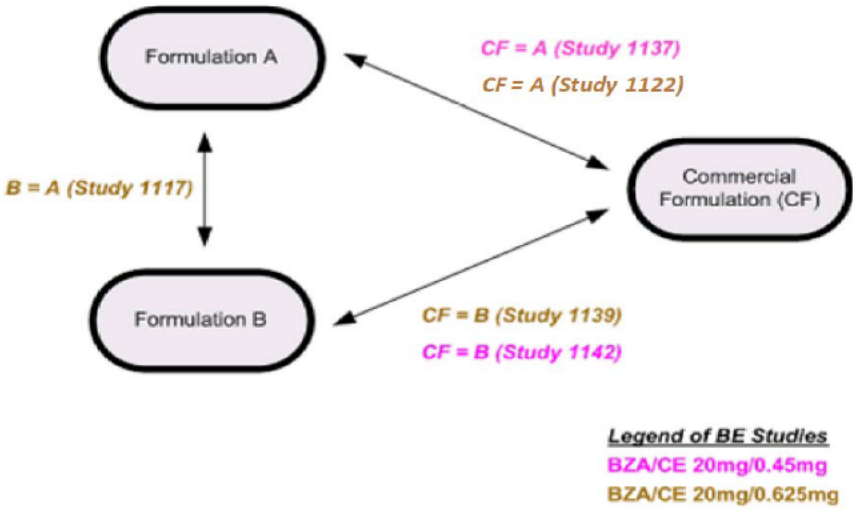
However, formulation C is the problem formulation in the entire program which was used in the major part of the clinical trial 304. The sponsor recognized the issue with formulation C and conducted another study (3115A1-**3307-WW**) similar to Study 304 using formulation A which is BE to TBM formulation D (see Medical Officer's review).

Figure 2.5.1.3 shows the time line of formulation and process development. This time line does not show the relationship between A vs C and A vs CF from Study 1117. Also, no relationship is shown from B vs C and C vs CF.

Figure 2.5.1.3: Formulation and Process Development History

The TBM formulation is manufactured at the Newbridge facility (b) (4) The BE of the BZA/CE 20/0.45 mg CF dose strength, manufactured at the commercial scale, for BZA and CE was demonstrated to clinical Formulation A in Study 3115A1-1137-US and to clinical Formulation B in Study 3115A1-1142-US (**Figures 2.5.1.3 and 4)**. It should be noted the majority of the CE components met the BE criteria but some did not in some of the studies (e.g., Study 1137). Similarly, the BE of the BZA/CE 20/0.625mg TBM dose strength, manufactured at the commercial scale, for BZA and CE was demonstrated to clinical Formulation A in Study 3115A1-1122-US and to clinical Formulation B in Study 3115A1-1139-US (**Figure 2.5.1.3 and 4).**

Figure 2.5.1.4: Bioequivalence Map linking Formulations A and B used in Pivotal Clinical Studies to the TBM Commercial Formulation (CF)



What is the Rationale for Formulation A?

The formulations used to select the dose strengths of BZA and CE used in Study 303 were a series of fixed-dose tablets containing combinations of 10, 20 or 40 mg of BZA, and 0.45 or 0.625 mg of CE. This series of formulations, designated as Formulation A, encompass the family of formulations that share a similar composition, but differ in the strength of BZA and CE.

(b) (4) Based on the outcomes of Study 303 at one year, the 20 mg BZA dose strength was chosen for further development.

(b) (4)

What is the Rationale for Formulation B?

(b) (4)

(b) (4)

(b) (4)

In 2004, pilot BA study (3115A1-109-US) was initiated (b) (4) Based on that study, there was no change in CE exposures. Therefore, studies 304, 305, and 306 were initiated in 2005 using Formulation B. Formulation B (20/0.625 mg) was demonstrated to be BE to Formulation A in study 3115A1-1117-US for most of CE components and BZA **(Figure 2.5.1.3**).

For Formulation B it was observed (b) (4) Based on this observation Formulation B was changed to Formulation C.

What is the Rationale for Formulation C?

(b) (4)

(b) (4)

The BA of Formulation C (20/0.625mg BZA/CE dose strength) relative to Formulation A was evaluated in four BA/BE studies (3115A1-114, 1120, and 1121, **Figure 2.5.1.3**). In all of the BA/BE studies in which CE was analyzed, most CE components of Formulation C was found to be BE to Formulation A, the reference formulation. (b) (4)

What is the Rationale for Formulation D (CF)?

The low BA of BZA with Formulation C led to efforts to optimize the formulation (b) (4)

(b) (4)

- (b) (4)
    - Study 311A1-1123-US: This study was conducted using 20/0.625mg strength (b) (4)
    - Study 3115A1-115-US: This is an earlier study for the same strength of 20/0.625 mg (b) (4)

The *in vitro* and *in vivo* relationship established in Study 1123 was used (b) (4)

(b) (4)

Table 2.5.1.2: Formulations Development Overview and Key Bioequivalence Studies

Formulation Type Development Start (year)	2001	2004	2006	2008
Formulation Type	A	B	C	CF
	(b) (4)			
Clinical Studies	303, 3307	304, 305, 306	304	N/A
Dose Strength (BZA/CE)	**Key BE Studies Linking Formulations A, B, C and CF**			
20/0.625mg	**B = A** (Study 1117)			
20/0.625mg		**C = B** (Study 1117)		
20/0.625mg	**C ≠ A** (Study 114, 1120, 1121, 1117)			
20/0.625mg	**CF = A** (Study 1122)			
20/0.45mg	**CF = A** (Study 1137)			
20/0.625mg		**CF = B** (Study 1139)		
20/0.45mg		**CF = B** (Study 1142)		

*In addition to the 20mg BZA dose strength, 10 and 40mg BZA doses of Formulation A were also evaluated in clinical Study 303.

Note: All subjects started Study 304 with BZA/CE Formulation B. After 3 to 9 months of treatment, subjects were transitioned to Formulation C. Subjects continued with Formulation C for the remainder of the study.

Table 2.5.1.3: 20/0.625 mg BZA/CE Formulation BA/BE Studies

Year --> 2004 2006 2007 2008 2009

	BE Studies on Formulations A, B, C and Commercial Formulation (CF) for the 20/0.625mg Dose Strength						
BA/BE Study Number	109	114	1120	1121	1117	1122	1139
BZA/CE Strength	40/0.625mg	20/0.625mg	20/0.625mg	20/0.625mg	20/0.625mg	20/0.625mg	20/0.625mg
Study Objective	Test PNP (b) (4) vs. PCP (b) (4) in BZA/CE tablets	BE Study Formulation C vs. A	BE Study C vs. A; Replicate design to account for BZA variability	BE Study C vs. A; Steady-state dosing	BE study across multiple formulation variants	Pivotal BE: Proposed CF vs. A	Pivotal BE: Proposed CF vs. B
Test Formulation(s)	Formulation B	Formulation C	Formulation C	Formulation C	Formulation B Formulation C	Commercial Formulation (CF)	Commercial Formulation (CF)
Reference(s)	Formulation A	Formulation A	Formulation A	Formulation A	Formulation A	Formulation A	Formulation B
GLS Mean Ratios for BZA Cmax (90% Confidence Interval)	-	84 (73-98)	78 (68-91)	68	90 (81-100) B vs A 98 (86-112) C vs B 88 (78-100) C vs A	98 (86-112) CF vs A	107 (95-121)
GLS Mean Ratios for BZA AUC (90% Confidence Interval)	-	78 (69-88)	74 (66-83)	64	88 (81-95) B vs A 93 (85-103) C vs B 82 (74-90) C vs A	101 (92-110) CF vs A	106 (96-116)
Study Outcome	CE (PNP) = CE (PCP)	C ≠ A	C ≠ A	C ≠ A	B = A, C = B C ≠ A	CF = A	CF = B

Notes:
PCP = Premarin current process: (b) (4)
PNP = Premarin new process: (b) (4)
CF = Commercial Formulation
Red text indicates these comparisons did not meet the BE confidence intervals of 80.00-125.00.

Table 2.5.1.4: 20/0.45 mg BZA/CE Formulation Pivotal BE Studies

	BE Studies on Formulations A, B and Commercial Formulation (CF) for the 20/0.45mg Dose Strength	
BA/BE Study Number	1137	1142
BZA/CE Strength	20/0.45mg	20/0.45mg
Study Objective	Pivotal BE: Proposed CF vs. A	Pivotal BE: Proposed CF vs. B
Test Formulation(s)	Commercial Formulation (CF)	Commercial Formulation (CF)
Reference(s)	Formulation A	Formulation B
GLS Mean Ratios for BZA Cmax (90% Confidence Interval)	98 (88-108) CF vs A	99 (87-113) CF vs B
GLS Mean Ratios for BZA AUC (90% Confidence Interval)	94 (88-101) CF vs A	99 (90-109) CF vs B
Study Outcome	CF = A	CF = B

Notes:
CF = Commercial Formulation

Reviewer's Comments:

As shown above, the biopharmaceutics program was too complex. The primary issue was with BZA PK parameters that did not meet the BE criteria in some of the studies (see individual study reviews, Section 4.2). The CE components in most of the studies met the bioequivalence criteria. Therefore, there was no issue with the release of CE components from the tablet.

The critical issue with BZA PK is that its systemic exposure appears to be important to the efficacy and especially for the safety (i.e., endometrial protection) considering its narrow therapeutic index. The low systemic exposure from Formulation C in the clinical trial 304 demonstrated a lower endometrial protection (see Medical Officer's review). In addition, high BZA systemic exposure is associated with venous thromboembolic events (VTEs) and stroke as (b) (4)

Overall BZA therapeutic window appears to be narrow in which any small change in the systemic exposure is associated with either loss of efficacy (i.e., endometrial protection from CE) or the development of VTEs. Therefore, it is critical that the systemic exposure of BZA remains relatively constant. Any intrinsic and extrinsic factors that may affect the absorption and metabolism of BZA should be carefully monitored and/or be avoided.

Conclusions on Formulations Bridging and Development:

Based on the above discussion (**Figures 2.5.1.3 and 2.5.1.4 and Tables 2.5.1.3-5**) the following conclusions can be made in terms formulation bridging/BE:

Formulation A is bioequivalent to CF for 20/0.625 mg strength (Study 1122)
Formulation A is bioequivalent to CF for 20/0.45 mg strength (Study 1137)
Formulation A is bioequivalent to B for 20/0.625 mg strength (Study 1117)
Formulation A is bioequivalent to B for 20/0.0.45 mg strength (Dissolution)
Formulation **A** is **not** equivalent to **C** for 20/0.625 mg strength (Studies 114, 1120, 1121, 1117)
Formulation B is bioequivalent to C for 20/0.625 mg strength (Study 1117)
Formulation B is bioequivalent to C for 20/0.45 mg strength (dissolution)
Formulation B is bioequivalent to CF for 20/0.625 mg strength (Study 1139)
Formulation B is bioequivalent to CF for 20/0.45 mg strength (Study 1142)
C vs CF (not assessed)

2.5.1 What is the Effect of Food on the BA of BZA/CE?

Overall, food appears to reduce the Cmax but slightly increased the AUC of BZA. However, there was no noticeable effect on CE.

This was based on a single-dose, crossover study to determine the effect of a high-fat meal on the relative BA and PK of BZA/CE in healthy postmenopausal women (Study 1116-US, Formulation C).

The study was designed as 3-period in 23 healthy postmenopausal women. The first 2 periods constituted the food effect portion of the study and subjects were given the BZA 20 mg /CE 0.625 mg (PNP) tablet in a fasting or fed state according to a randomized sequence. In the third period, all subjects were given the BZA 20 mg/CE 0.45 mg (PNP) strength tablet in a fasting state. There was a 10-day washout between each of the three treatments.

Treatment A (Fasting):	Single dose of BZA/CE (PNP) 20mg/**0.625** mg administered under **fasting** conditions
Treatment B (Fed):	Single dose BZA/CE (PNP) 20mg/**0.625** mg administered 5 minutes after completion of the FDA recommended **high-fat breakfast**
Treatment C (Fasting):	Single dose BZA/CE (PNP) 20mg/**0.45** mg administered under **fasting** conditions

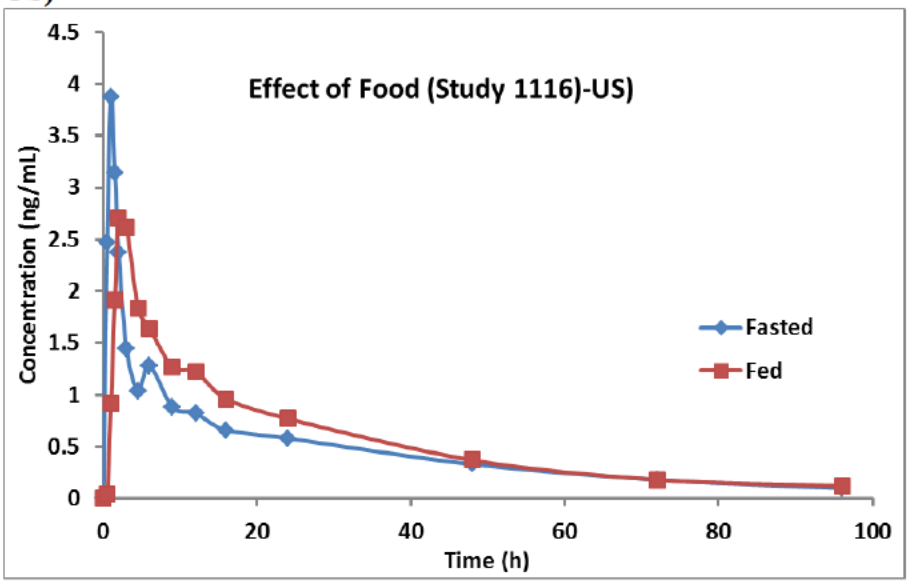
Blood samples for BZA/CE PK analysis were collected at adequate intervals over 96 hours.

The BZA PK data are summarized in **Table 2.5.1.1** and **Figure 2.5.1.1.**

Table 2.5.1.1: BZA PK Parameters after Administration of BZA 20 mg/CE 0.625 mg under Fasting and Fed Conditions

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Fasting)	Mean±SD	4.25±2.48	1.4±1.0	28.8±8.6	43.7±21.9	48.2±24.3
	%CV	58.3	74.3	29.9	50.0	50.4
	N	23	23	23	23	23
	Geometric Mean	3.26	1.2	27.6	38.2	42.3
	(Range)	(0.37-8.43)	(0.5-4.5)	(18.1-49.7)	(12.3-107)	(13.8-118)
1 BZA 20 mg/ CE 0.625 mg Tablet (Fed)	Mean±SD	4.12±3.34	3.4±2.3	26.2±5.8	53.0±25.1	57.6±26.1
	%CV	81.0	68.4	22.0	47.3	45.4
	N	23	23	23	23	23
	Geometric Mean	3.26	2.9	25.7	48.5	52.8
	(Range)	(1.00-14.2)	(1.0-12.0)	(18.8-38.8)	(21.0-131)	(22.6-135)
p-Values of Fixed Effects from the Mixed-Effects Model of Log-Transformed Pharmacokinetic Parameters						
Source of Variation						
Sequence		0.381	0.600	0.792	0.007	0.010
Treatment		0.998	<0.001	0.101	0.128	0.134
Period		0.889	0.499	0.922	0.848	0.836
Statistical Power (%)		13.2	24.9	-	29.5	32.3
GLS Means Ratio and CLs[a]						
GLS Means Ratio		100	247	-	127	125
90% CL		64-156	186-329	-	98-164	98-159

Figure 2.5.1.1: Mean BZA Plasma Concentrations-Time Profiles Following Administration of a Single 20 mg/0.625 mg Dose of BZA/CE (PNP) under Fasting and Fed Conditions (Study 1116-US)



Reference ID: 3319890

The BA of BZA from a BZA 20 mg/CE 0.625 mg tablet was greater when the tablet was administered following a high-fat breakfast than when administered under a fasting condition. The mean Cmax of BZA was slightly reduced when taken with food, but AUC was approximately 27% greater. In addition, the administration of BZA/CE after a high-fat breakfast delayed the tmax of BZA to 3.4 hours compared with 1.4 hours under a fasting condition.

In contrast to the differences observed with BZA, food appeared to have little effect on the PK of the estrogens. For both total and unconjugated estrone and equilin, the extent of absorption (AUC) was comparable between the fed and the fasting subjects (**see Section 4.2 for individual study review**).

2.5.2 Are the method and dissolution specifications supported by the data provided by the sponsor?

CE Proposed Dissolution Method:

The method proposed for *in vitro* dissolution for BZA/CE is summarized in **Table 2.5.2.1** in comparison to the established Premarin® dissolution method:

Table 2.5.2.1: Comparison of CE Dissolution Method Conditions for BZA/CE Tablets and PREMARIN Tablets

	BZA/CE CE Dissolution Method STM-00003181 (L27576-087)	PREMARIN CE Dissolution Method L22115-001
Apparatus	USP Apparatus 2 (Paddles) at 50 RPM	USP Apparatus 2 (Paddles) at 50 RPM
Media	0.9 L Water with 0.1% SLS	0.9 L of pH 4.5 acetate buffer
Temperature	37 °C	37 °C
Sinkers	No	Yes
Detection & Quantitation	HPLC with UV detection	HPLC with UV detection

BZA Proposed Dissolution Method:

The bio-relevance of proposed commercial method for BZA dissolution has been demonstrated with several clinical studies.

ONDQA will assess the adequacy of the final methods and specifications.

2.3 Analytical Section

BZA Assay:

The analytical method for the determination of the plasma BZA and its metabolites was already reviewed and accepted by the Office of Clinical Pharmacology (see original OCP review dated March 21, 2007)

Briefly, this was a high performance liquid chromatography (HPLC)-fluorescence and liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation was 25 pg/mL.

It should be noted that several HPLC methods with fluorescence detection were initially developed and validated for the quantitation of BZA in plasma. (b) (4)

HPLC/fluorescence methods were also developed for the quantitation of total (conjugated and unconjugated) BZA in plasma. Liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods for the quantitation of BZA in plasma were also developed and used later in the BZA/CE development program. The LLOQ for all these methods ranged from20 pg/mL to 250 pg/mL (depending on the plasma volume used (0.2 mL to 1 mL).

The analytical methods (GC/MS/MS) for the determination of CE and its metabolites are well established at many laboratories and in the literature. The LLOQ for all CE components ranges from 2.5 pg/mL for 17β-estradiol to 25 pg/mL for estrone.

3.0 Labeling Comments (preliminary):

Labeling comments will be made directly into the label during the internal labeling meetings.

Reference ID: 3319890

4.0 Appendices

4.1 Sponsor's Proposed Label
4.2. Individual Study Review (Selected Studies)
4.3 Consult Reviews:
4.3.1 Pharmacometric Review
4.4 Filing memo

4.1 Sponsor's Proposed Label

(b) (4)

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Individual Study Review (Selected Studies)

See separate file in DARRTS.

4.3.1 Pharmacometric Review

SUMMARY OF FINDINGS

The proposed dosing regimen BZA 20 mg/CE 0.45 mg is acceptable from the pharmacometric perspective. The BZA dose of 20 mg is the minimum effective dose among the tested doses when combined with 0.45 or 0.625 mg CE. Low BZA dose of 10 mg failed to provide adequate endometrial protection, and higher BZA dose of 40 mg caused unacceptable efficacy loss.

Except for endometrial protection and improved tolerability, BZA did not show positive contribution to the three estrogenic efficacy endpoints (VMS, VVA, and Prevention of Osteoporosis). Instead, it attenuated the desired treatment effect in a dose-dependent manner. The higher the BZA dose, the greater the estrogenic efficacy loss was observed. When BZA dose was 40 mg, no significant difference was shown for VMS and VVA between BZA/CE and the placebo groups.

One prominent challenge of using BZA/CE was how to optimize BZA exposure. (b) (4) In this regard, subjects with significantly high clearance to BZA due to intrinsic or extrinsic factors may be at risk of underexposure and more likely to develop hyperplasia. BZA did not show narrow therapeutic index for endometrial protection when combined with low CE dose of 0.45 mg (Figure 16).

(b) (4)

Key Review Questions

The purpose of this review is to address the following key questions:

Is there any evidence of dose-response relationship for BZA in endometrial protection?

BZA demonstrated clear dose-dependent effect in endometrial protection. The rate of endometrial hyperplasia decreased with increased BZA doses. Larger effect was observed in patients treated with lower dose of CE, suggesting that the effect of BZA was dependent on the CE dose. As shown in **Table 1**, in study 303, after 12 months of treatment, the 40 mg dose of BZA showed a full protection of endometrium under the studied sample size when combined with either 0.625 mg or 0.45 mg of CE. There was no endometrial hyperplasia case observed. For a reduced dose of 20 mg BZA, the complete protection was only achieved at the low dose of CE (0.45 mg), (b) (4) The protection was further reduced to an unacceptable level when the dose of BZA was lowered to10 mg. In terms of endometrial protection, BZA 20 mg may be considered the minimum effective dose

that will produce an acceptable rate of hyperplasia when combined with 0.45 or 0.625 mg CE. This result is consistent with findings from study 203, a Phase II, dose-finding study.

Table 1: Incidence of Endometrial hyperplasia at Month 12

(Study 3115A1-303, Efficacy Evaluation Population)

Treatment Group[a]	N	n	Incidence of Hyperplasia (%)	CI[b]
CE 0.45 mg with:				
40 mg BZA	309	0	0.00	(0.00 – 1.19)[c]
20 mg BZA	335	0	0.00	(0.00 – 1.10)[c]
10 mg BZA	320	3	0.94	(0.26 – 2.41)
CE 0.625 mg with:				
(b) (4)				
Raloxifene 60 mg	298	0	0.00	(0.00 – 1.00)
Placebo	312	0	0.00	(0.00 – 0.96)

n = number of subjects with hyperplasia at any time during the study up to and including month 12.

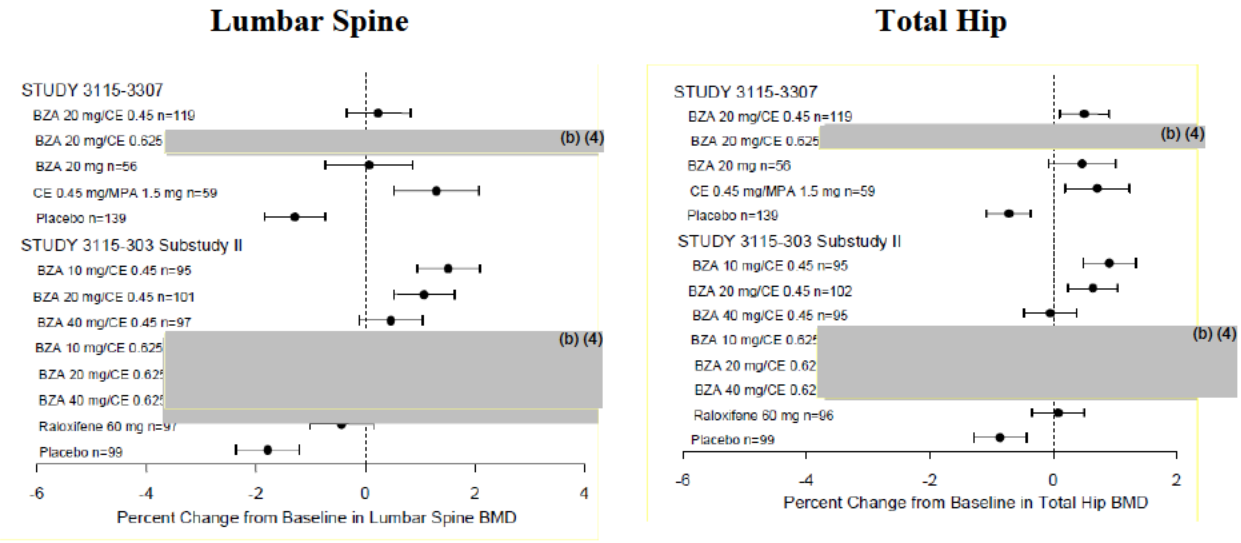
Source: Table 9-2 on page 103 of sponsor's report 3115A1-303-US/EU/BR

However, it is worth noting that study 304 did not show acceptable endometrial protection. The observed hyperplasia rate in the BZA 20 mg/ CE 0.625 mg group was more than (b) (4) The rate at 12 months was much higher than those observed in study 303 (b) (4) and study 3307 (b) (4)) in subjects receiving the same treatment (BZA 20 mg/ CE 0.625 mg). The rate was even higher after 24 months or using FDA's definition of hyperplasia. (b) (4)

Is there any evidence of dose-response relationship for BZA in the prevention of post-menopausal osteoporosis?

BZA did not show synergistic benefit in preventing bone loss when combined with CE. Instead, it attenuated the preventive effect of CE in postmenopausal osteoporosis. After BZA/CE treatment for 12 months, lumbar spine and total hip bone density decreased with increased BZA doses (Figure 1). Despite the induced efficacy loss by BZA, the BZA/CE combination remained effective in preventing postmenopausal bone loss. The proposed dosing regimen (BZA 20 mg/ CE 0.45 mg, BZA 20 mg/CE 0.625mg) demonstrated significantly better effect than the placebo, as well as the approved drug in the same class, raloxifene (60 mg).

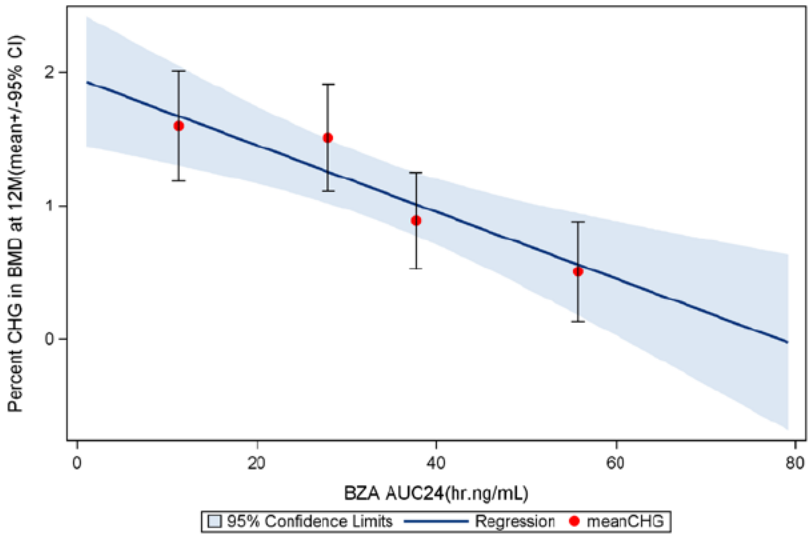
Figure 1: Percentage Change from Baseline (95% CI) to Month 12 in BMD of Lumbar Spine and Total Hip (MITT Population, LOCF)



Source: Figure 3-9 (Lumbar Spine) and Figure 3-10 (Total Hip) in sponsor's ISE report

A plot of change in spine BMD at Month 12 versus BZA exposure (population PK model-estimated AUC) in patients from study 303 and 304 confirmed the attenuating effect of BZA in preventing bone loss under BZA/CE treatment. Higher BZA exposure was associated with lower bone density (Figure 2).

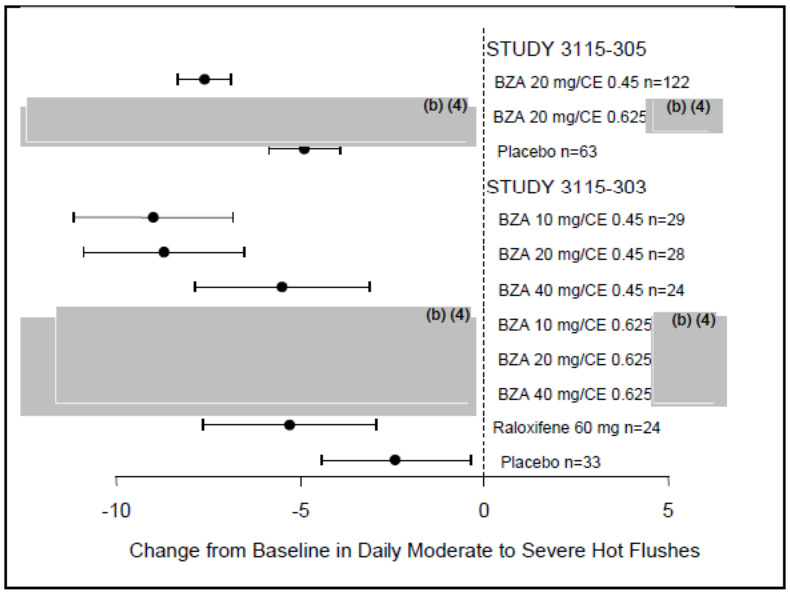
Figure 2: Relationship between change in lumbar spine bone mineral density at Month 12 vs. BZA exposure (study 303 and 304 combined)



Is there any evidence of dose-response relationship for BZA in the treatment of VMS?

In study 305, the proposed BZA 20 mg/ CE 0.45 mg and BZA 20 mg/ CE 0.625 mg treatments were statistically more effective than the placebo group (p<0.001) and raloxifene 60 mg (p=.032) in the management of hot flushes after 12 weeks. However, BZA did not show additional benefit when combined with CE. By contrast, BZA reduced CE effect in a dose-dependent manner. As shown in Figure 3, in Study 303, higher dose BZA was associated with higher number of daily number of moderate and severe hot flushes. (b) (4)

Figure 3: Percent Change from Baseline (95% CI) in Number of Moderate and Severe Hot Flushes at Week 12: Study 305 (MITT, LOCF) and Study 303 (EE1, LOCF) (MITT, LOCF)



Source: Figure 3-1 on Page 137 of sponsor's ISE report

Is there any evidence of dose-response relationship for BZA in the treatment of VVA?

(b) (4)


(b) (4)
(4)
20


(b) (4)


(b) (4)


(b) (4)

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

PERTINENT REGULATORY BACKGROUND

This original NDA (022247) proposes a combination of BZA) with CE in a tablet that consists of BZA 20 mg /CE 0.45 mg or BZA 20 mg/CE 0.625 mg for the treatment of postmenopausal symptoms, including moderate to severe VMS, moderate to severe symptoms of VVA, and prevention of postmenopausal osteoporosis, in women with an intact uterus. CE (Premarin®) has been marketed in the U.S since 1942 and in the EU since the early 1950s for the treatment of menopausal symptoms and the prevention of osteoporosis. BZA is a new molecular entity and a third generation selective estrogen receptor modulator (SERM) being developed by Wyeth and now by Pfizer. It was approved in the EU in 2009 and Japan and some other countries for the treatment of postmenopausal osteoporosis (b) (4)

The clinical development program designed to support efficacy and safety in this application included 26 clinical trials (20 Phase 1, 1 Phase 2, and 5 Phase 3 studies). The safety database included 7271 women, of whom 4828 were exposed to BZA/CE. Data from previous BZA monotherapy NDAs were also available for review if needed.

RESULTS OF SPONSOR' S ANALYSIS

Population PK/PD analysis:

OBJECTIVES:

The primary objective of the sponsor's analyses was to develop a population PK model to describe concentration time data of BZA in postmenopausal women to identify and characterize factors that influence the PK of BZA. The sponsor developed two population PD models. One was to describe the relationship between BZA exposure and risk of developing endometrial hyperplasia in postmenopausal women. The other was to evaluate the relationship between BZA exposure and changes in bone mineral density (BMD) in post-menopausal women.

DATABASE:

PK Database: The PK data used in the present population PK analysis represent all available concentration data collected in Studies 108, 114, 1120, 1121, 203, 300, 303, and 304. Initially these data were to be pooled into a single database for evaluation. Initial attempts to model data from all studies together were unsuccessful and these studies were split into a dense PK database (containing data from Studies 108, 114, 1120, and 1121) and a sparse PK database (containing data from Studies 203, 300, 303, and 304) and were modeled separately. The final dense database used for modeling and evaluation consisted of 7425 observation from a total of 237 subjects. The final sparse database for modeling consisted of 3025 observation from a total of 1823 subjects. There was an average of 1.7 observations per subject in the sparse database. The summary of baseline demographics for the dense and sparse datasets is as follows:

Table 2: Summary of Baseline Demographics for the Dense PK Database (n=237)

Demographic (units)	Mean (SD)	Median	Range
Age (y)	57.2 (6.13)	58	38-70
Height (cm)	164 (6.08)	164	148-181
Weight (kg)	74.4 (10.8)	74.3	47.2-103
CrCL (mL/min)	96.1 (19.9)	98	44.4-150
ALT (IU)	34.5 (14.6)	35	8-84
AST (IU)	21.4 (6.56)	20	11-69
Bilirubin (mg/dL)	7.66 (3.43)	6.84	1.71-29.1
Triglyceride	1.48 (0.75)	1.31	0.35-4.91
Study	108 = 23; 114 = 72; 1120 = 72;1121 = 70		
Dose	5 mg = 23, 20 mg = 237, 40 mg = 23		
Formulation	Single Agent = 23, Formulation A=214, Formulation C=214		
Premarin	Not taking = 23; taking = 214		
Race	Caucasian = 190; Non-Caucasian = 47		

Table 3: Summary of Baseline Demographics for the Sparse PK Database (n=1823)

Demographic (units)	Mean (SD)	Median	Range
Age (y)	55.1 (5.71)	54	40-82
Height (cm)	163 (6.63)	163	141-183
Weight (kg)	68.2 (10.7)	67.6	38.4-105
CrCL (mL/min)	88.7 (21.8)	86.3	34.1-216
ALT (IU)	22.7 (9.25)	21	5-74
AST (IU)	22.9 (5.98)	22	6-53
Bilirubin (mg/dL)	9.24 (3.83)	8.55	2.8-29.1
Triglyceride	1.21 (0.61)	1.06	0.305-5.55
Study	203 = 253; 300 = 783; 303 = 467; 304 = 320		
Dose	5 mg = 109, 10 mg = 482; 20 mg = 833, 40 mg = 399		
Formulation	Single Agent = 1036, Formulation A=467, Formulation C=320		
Premarin	Not taking = 0; taking = 1823		
Race	Caucasian = 1614; Non-Caucasian = 209		

PD Database:

Exposure/Endometrial Hyperplasia Database: This database was constructed using data from studies 303, 304, and the HOPE study. Subjects with individual PK parameter estimates for BZA from studies 303 and 304 were included in this study. BZA AUC was calculated for all subjects enrolled in study 303 and 304 using function AUC=DOSE/CL. The HOPE subjects did not receive BZA and thus served as the background rate of hyperplasia for both CE given as a single agent and placebo. The final database used for model building and evaluation consisted of 1845 observations from a total of 1845 subjects (Table 4).

Table 4: Baseline Demographics for the Hyperplasia Analysis (n=1845)

Demographic (units)	Mean (SD)	Median	Range
Age (y)	53.2 (4.22)	53	40-64
Weight (kg)	68.2 (11.2)	67.7	38.4-105
BZA AUC	36.36 (13.8)	35.1	5.9-79.2
Dose CE	0 mg = 261; 0.3 mg = 269; 0.45 mg = 663; 0.625 mg = 652		
Dose BZA	0 mg = 797; 10 mg = 154; 20 mg = 491; 40 mg = 142		
BZA Formulation	Formulation A=449; Formulation B/C=338; no BZA = 797		

Spine BMD Disease Progress Database:

The spine BMD measurements from 995 subjects were from study 303 and 304. The final spine BMD database used for modeling consisted of 3671 spine BMD observation from a total of 968 subjects (Table 5). There were 3.8 spine BMD observations per subject on average in this sparse database.

Table 5: Baseline Demographics for the Spine BMD Disease Progression

Demographic (units)	Mean (SD)	Median	Range
Age (y)	52.5 (3.63)	53	41-64
Height (cm)	162 (7.04)	162	141-183
Weight (kg)	67.9 (10.8)	67.6	38.4-105
CrCL (mL/min)	92.3 (24.8)	87.9	34.1-216
ALT (IU)	22.7 (9.44)	21	5-74
AST (IU)	22.9 (5.65)	22	11-53
Bilirubin (mg/dL)	9.62 (4.05)	8.55	3.42-29.1
Triglyceride	1.22 (0.63)	1.08	0.304 – 5.55
BZA AUC	36.6 (14.9)	35	5.9-79.2
Study	303 = 705; 304 = 263		
BZA Dose	0 mg = 358, 10 mg = 146; 20 mg = 327, 40 mg = 138		
Formulation	Formulation A=430, Formulation C=181		
CE	0.45 mg = 299; 0.624 mg = 312		
Race	Caucasian = 510; Non-Caucasian = 458		

Hip BMD Disease Progression Database:

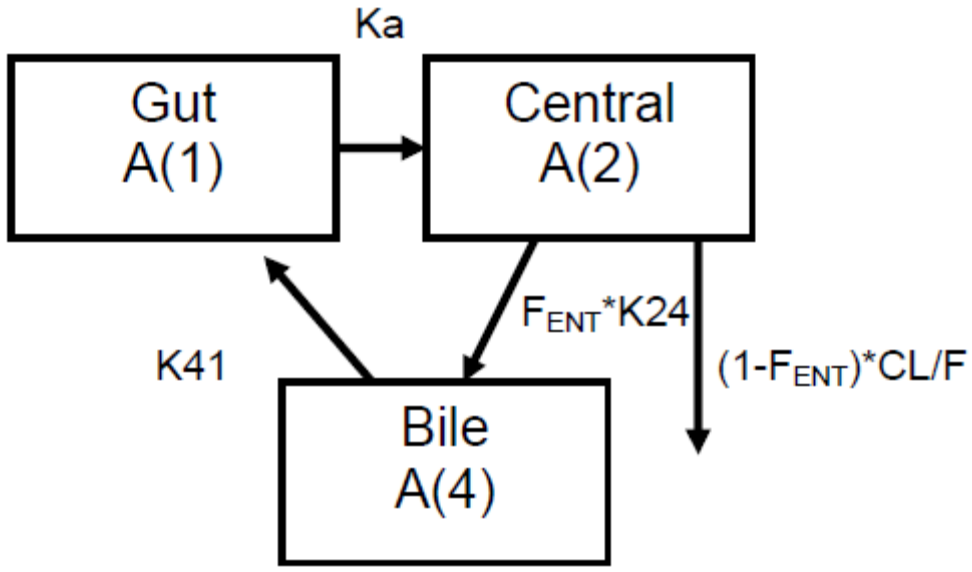
The hip BMD measurements were from study 303 and 304.

The final database used for model building and evaluation consisted of 3863 hip BMD observations from a total of 1016 subjects, There were 3.8 BMD observations per subject on average in this sparse database. A summary of the demographic information for the hip database is presented in Table 6.

Table 6: Baseline Demographics for the Hip BMD Disease Progression Analysis (n=1016)

Demographic (units)	Mean (SD)	Median	Range
Age (y)	53.5 (4.79)	53	40-73
Height (cm)	160 (15.9)	162	141-183
Weight (kg)	67.4 (12.4)	67.5	38.4-105
CrCL (mL/min)	91.7 (25.9)	87.9	34.1-216
ALT (IU)	22.5 (9.56)	21	5-74
AST (IU)	22.6 (9.55)	22	11-53
Bilirubin (mg/dL)	9.48 (4.10)	8.55	3.42-29.1
Triglyceride	1.21 (0.63)	1.07	0.304 – 5.55
BZA AUC	22.7 (21.2)	22.1	5.9-79.2
Study	303 = 741; 304 = 276		
BZA Dose	0 mg = 378, 10 mg = 154; 20 mg = 343, 40 mg = 142		
Formulation	Formulation A=444, Formulation C=195		
CE	0.45 mg = 312; 0.624 mg = 327		
Race	Caucasian = 832; Non-Caucasian = 184		

Figure 6: General Schematic Diagram of BZA PK Model



Source: Figure 2 on Page 47 of sponsor's report

3.1.1 Population PK Model-Dense Data

The best final PK model for BZA was a one compartment model with first order input following a lag time and linear elimination. In addition, the model incorporated enterohepatic recycling and was evaluated using ADVAN6 and TRANS1. The model was parameterized for a lag time prior to absorption (ALAG), the first order absorption rate constant (ka), the apparent clearance (CL/F), and the apparent volume of distribution of the central (V2/F). The equations for the parameters describing this model are shown below. The general schematic diagram for this model is given in Figure 6, and the parameters for the final dense data model were summarized in Table 7.

Equations for population PK model of dense data:

Reference ID: 3319890


(b) (4)


(b) (4)

Table 7: Parameter Estimates for Final BZA PK Model-Dense Database

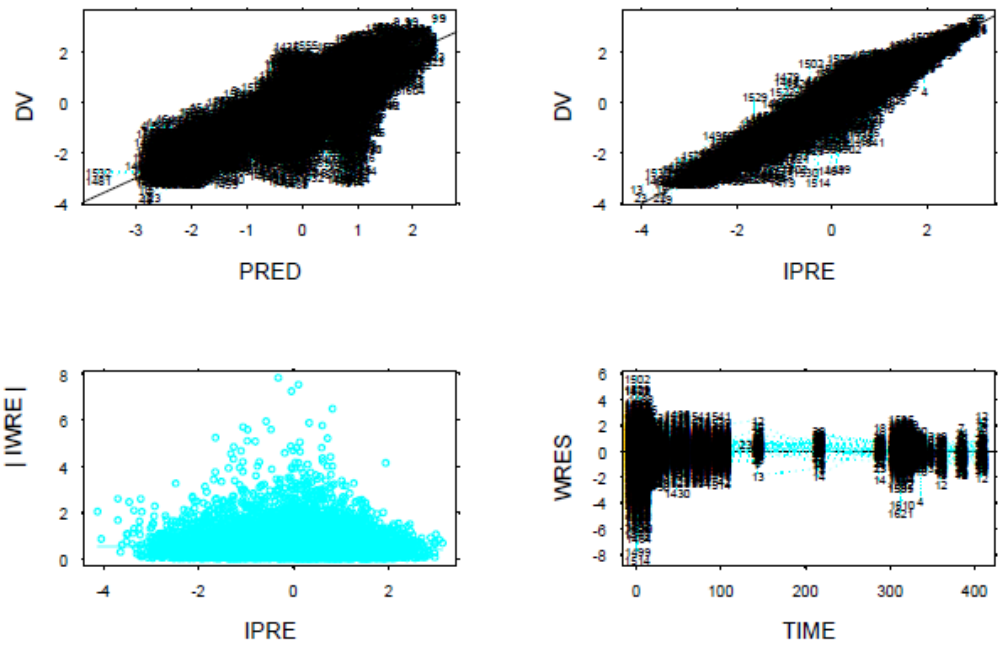
Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h)	Θ_1	1350 (11.7)	40.7 (23.7)
Effect of weight		0.75 FIX	
Effect of ALT	Θ_{10}	0.202 (52.0)	
V2/F (L)	Θ_2	3460 (17.6)	94.7 (65.6)
Effect of weight		1 FIX	
Effect of race	Θ_{11}	0.61 (12.3)	
Ka (1/h)	Θ_3	2.27 (34.2)	134 (31.6)
ALAG (h)	Θ_4	0.385 (3.8)	24.4 (50.3)
FENT (%)	Θ_5	1.09 (8.9)	28.6 (25.8)
TENT (h)	Θ_6	2.11 (23.9)	NE
K41 (1/h)	Θ_7	0.139 (7.3)	13.9 (20.0)
F1A	Θ_8	0.851 (10.0)	19.7 (75.0)
F4A	Θ_9	0.686 (10.6)	57.4 (13.2)
CCV Residual Error (as %CV)		36.3 (3.6)	

* - SE given as %CV; NE - Not Estimated

Diagnosis of Final PK model-Dense Data

The overall goodness-of-fit plots are shown in Figure 7. There were no visual bias in the population and individual predicted concentrations. There were no trends in the loess smooth of the data.

Figure 7: General Goodness of Fit Plots-Final PK Model



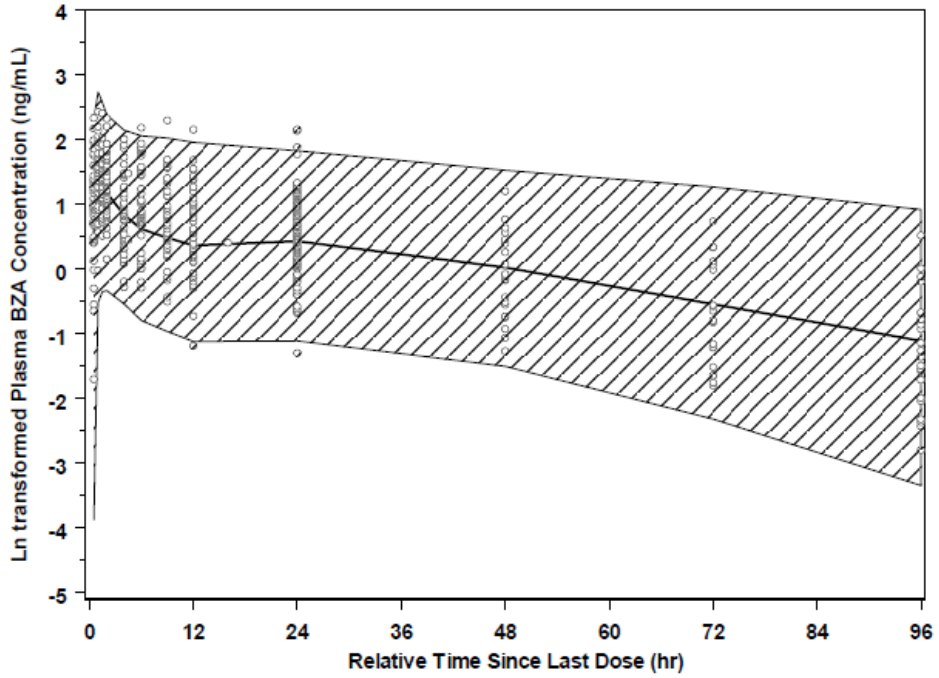
Source: Figure 14 on page 283 of sponsor's report

Visual Predictive Check for Concentration Time Profile

Reference ID: 3319890

The plot for the visual predictive check is shown in Figure 8. The plots showed the 2.5th, 50th, and 97.5th prediction intervals. It can be seen that the majority of the observed BZA concentrations fall between the 95% prediction intervals. Overall the predictive performance of this model was considered adequate.

Figure 8: Visual Predictive Check for Final PK Model-Dense PK Database 20 mg Dose Formulation 1



Source: Figure 14 on page 59 of sponsor's report

3.1.2 Population PK Model-Sparse Data

The best final PK model for BZA in the sparse data was a one compartment model with first order input following a lag time and linear elimination. The model also incorporated enterohepatic recycling. The model was parameterized for a lag time prior to absorption (ALAG), the first order absorption rate constant (Ka), the apparent clearance (CL/F), the apparent volume of distribution (V2/F). No covariate factors were identified.

The equations for the parameters describing this model are shown below. The equations are consistent with the structural model for the dense data. The estimates of final parameters for the final model are summarized in Table 8. The general goodness-of-fits plot is demonstrated in Figure 9 and the visual predictive check for the final model is in Figure 10:

Reference ID: 3319890

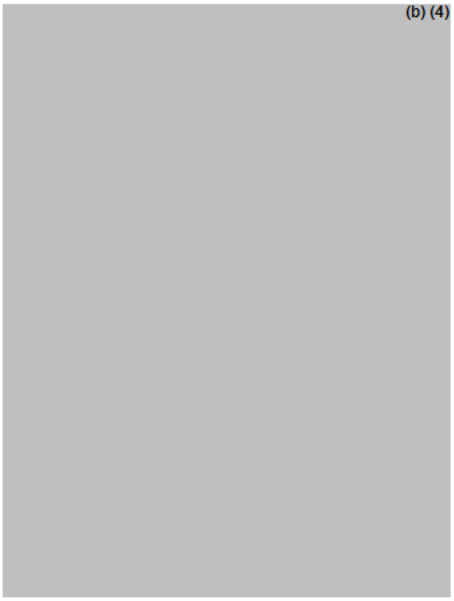
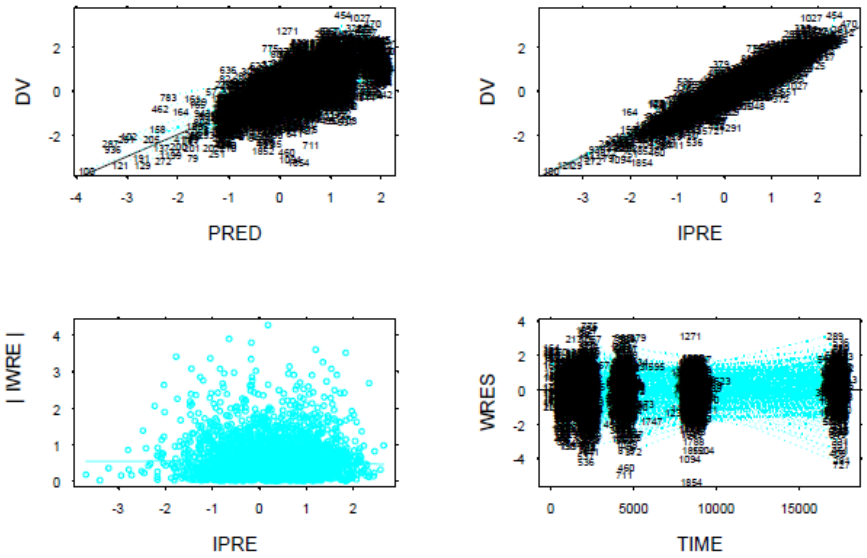


Table 8: Parameter Estimates for Final PK Model-Sparse Database All Data

Parameter (Units)		Population Mean	%CV Inter-Individual Variance
CL/F (L/h)	Θ_1	1790	45.9
V2/F (L)	Θ_2	5610	110
Ka (1/h)	Θ_3	2.4 FIX	NE
ALAG (h)	Θ_4	0.39 FIX	NE
FENT (%)	Θ_5	1.12 FIX	NE
TENT (h)	Θ_6	2.2 FIX	NE
K41 (1/h)	Θ_7	0.14 FIX	NE
F1A	Θ_8	1.07	22.8
F4A	Θ_9	0.962	53.8
CCV Residual Error (as %CV)		42.7	

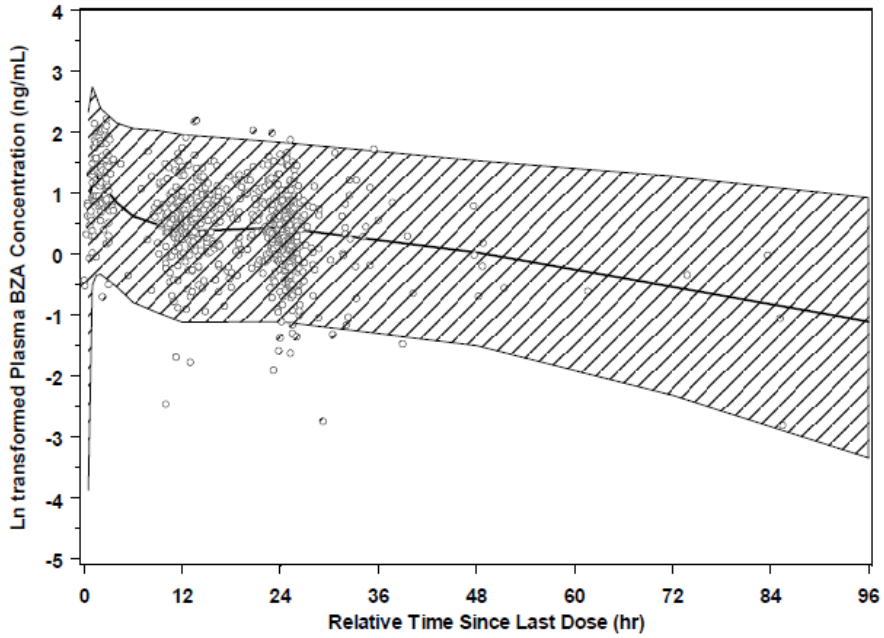
NE - Not Estimated

Figure 9: General Goodness of Fig Plots-Final PK Model All Data



Source: Figure 12 on page 551 of sponsor's report.

Figure 10: Visual Predictive Check for Final PK Model-Sparse PK Database 20 mg Dose Formulation 1 All Data



Exposure- Endometrial Hyperplasia-Logit Analysis

The sponsor explored exposure-endometrial hyperplasia relationship using logit analysis. The best final model for the probability of developing hyperplasia was a binomial logistic regression including the effects of CE dose, BZA AUC normalized by relative bioavailability of the formulation given and weight. The equations for the parameters describing the best logit model

are shown below. The estimated parameters for this model are summarized in Table 9. The diagnostic plots by CE dose are presented in **Figure 11.**

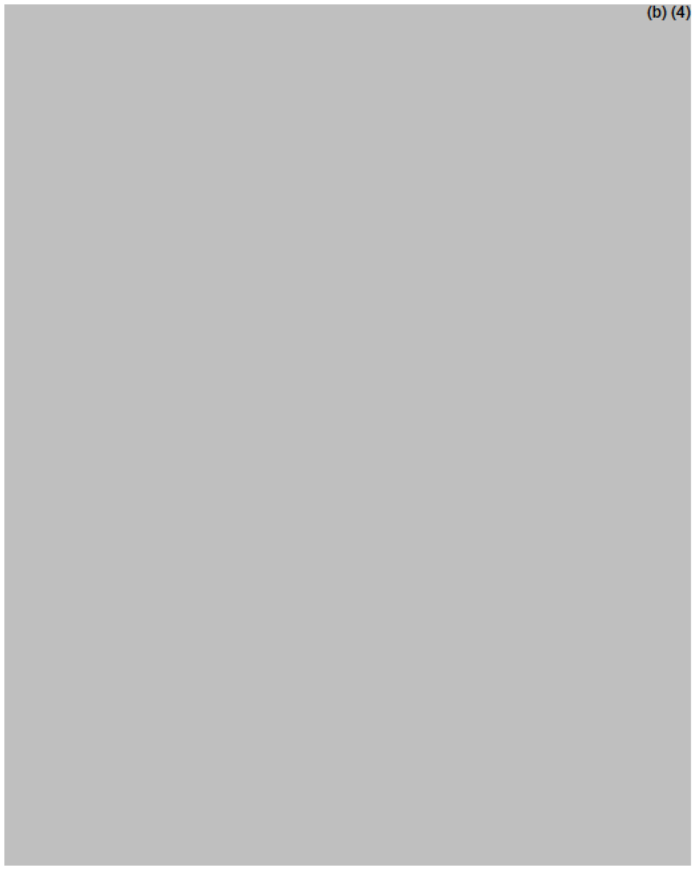


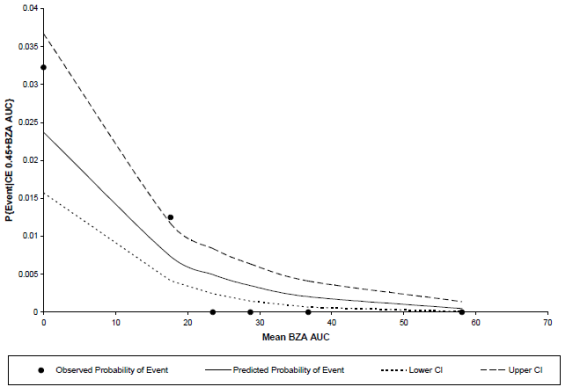
Table 9: Parameter Estimates for Final Logit Model-Exposure/Endometrial Hyperplasia Database

Parameter		Population Mean (SE*)	Bootstrap 95% CI
BaseP	Θ_1	0.000504 (84.7)	0.000199-0.00261
Fac	Θ_2	0.861 (16.8)	0.569-1.05
Fac2	Θ_3	0.673 (18.7)	0.479-0.983
SDodd	η_1	0 Fixed	NE

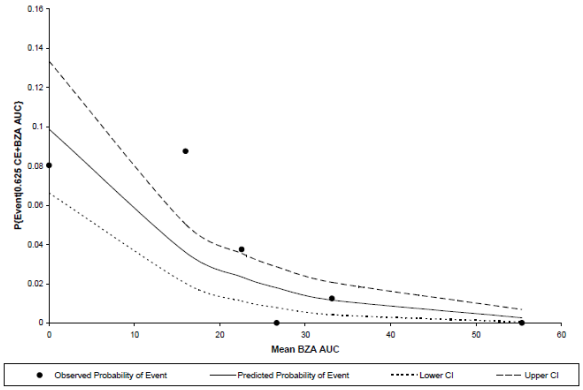
* - SE given as %CV; NE - Not Estimated

Figure 11: Observed and Predicted Probability of Event and Associated 95% Confidence Intervals for 0.45 CE (Left) and 0.625 CE (Right) Dose-Final Logit Model

CE = 0.45 mg



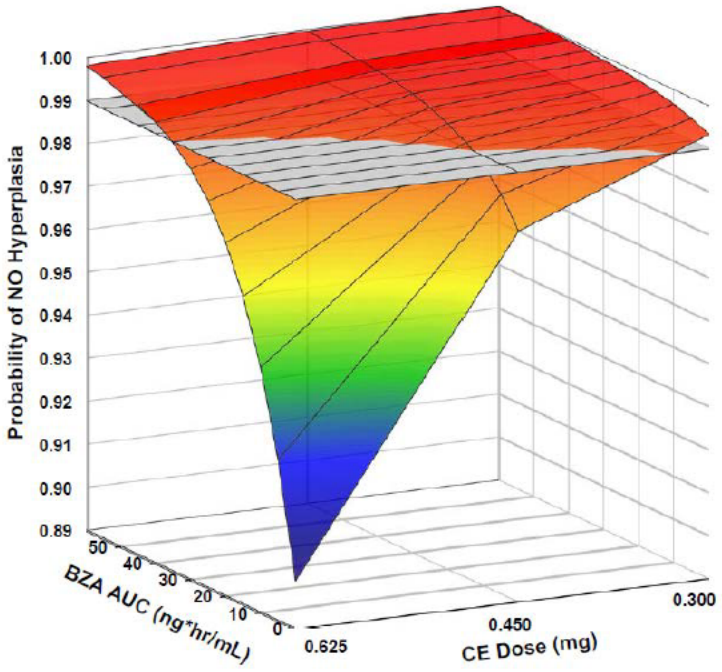
CE= 0.625 mg



Source: Figure 37 (left) and Figure 39 (right) of sponsor's report

As demonstrated in Figure 12, the sponsor made a 3D surface plot that described overall hyperplasia probability for a no event over a range of CE doses and BZA AUC values. In order to maintain a probability of hyperplasia with a dose CE of 0.625 mg at less than 1%, the BZA AUC must be at least 35 ng*hr/mL. For a CE dose of 0.45, the BZA AUC must be at least 15 ng*hr/mL.

Figure 12: Surface Plot of Probability of No Hyperplasia by CE Dose and BZA AUC-Final Logit Model



BMD Disease Progress Analysis

The sponsor developed BMD disease progress models for both the spine and the hip database. The final model for the spine BMD data was a linear model with variance terms on slope and intercept. The model also included a sine function to describe the seasonal changes in BMD. This model included the effects of BZA dose and had an effect of normalized weight on the intercept. The equations for the parameters describing the Final Spine BMD model are shown below. The estimated parameters are summarized in Table 10 and the diagnostic plots are in Figure 13.

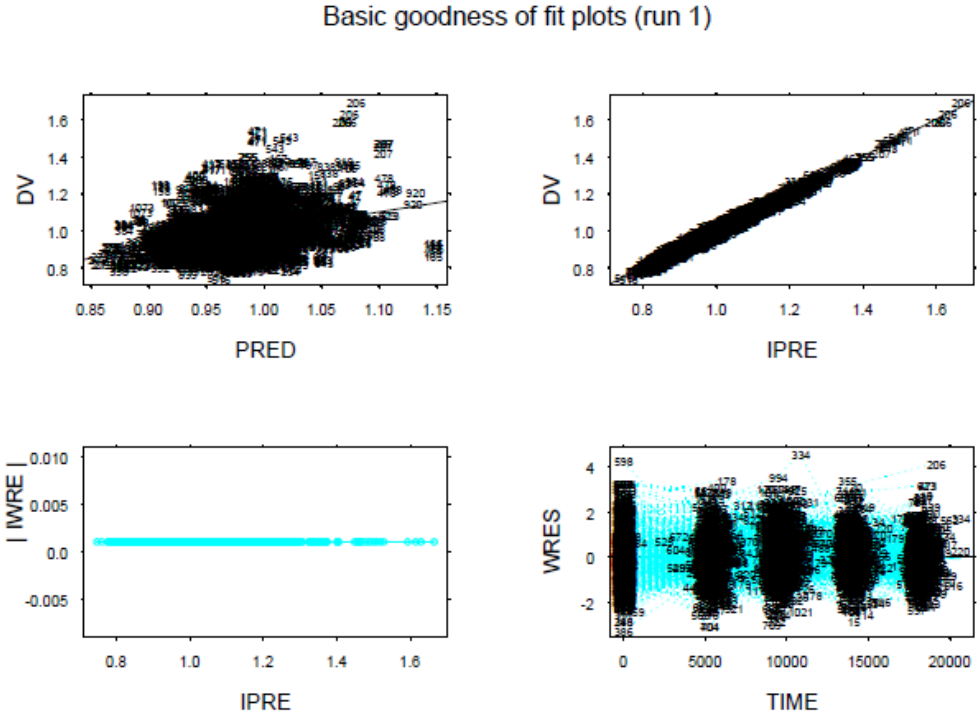
(b) (4)

Table 10: Parameter Estimates for Final Spine BMD Model

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
S0 (g/cm^2)	Θ_1	1.0 (0.375)	10.8 (4.6)
Effect of weight on S0	Θ_2	0.217 (12.8)	0.00109 (9.6)
Slope (g/cm^2/month)/10000	Θ_3	8.57 (10.5)	NE
Effect of BZA Dose on slope	Θ_4	0.301 (22.6)	NE
Amplitude	Θ_5	0.00226 (24.4)	NE
Omega	Θ_6	106 (0.1)	NE
Phase	Θ_7	10.9 (6.3)	NE
Additive Residual Error			0.0176 (2.8)

* - SE given as %CV; NE - Not Estimated

Figure 13: General Goodness of Fit Plots-Best Spine BMD Model



Reviewer's Comment on the sponsor's population PK/PD analysis

1. *The population PK model for the dense database is adequate in describing the observed data.*
2. *The individual AUCs for study 303 based on the population PK model for the sparse database may not be reliable. The study did not contain a planned PK component. Retained blood sample were assayed for BZA concentration after the sponsor realized the importance of the BZA exposure due to the failure of study 304. As a result, the actual time of the sampling relative to the dose time was not recorded and a fixed time-after-dosing was assumed for all patients. In addition, most subjects had only one blood sample in study 303. Even though the trend of the PK/PD analyses is consistent with the expectation and the dose-response observations, the parameter estimates may not be accurate due to the unreliable AUC estimates.*
3. *The reviewer conducted independent logistic analysis using corrected doses based on the different bioavailability between formulations A and C. The results are shown as follows*

REVIEWER'S ANALYSIS

Introduction

The results from population PK analysis indicated that a 30% reduction in BZA exposure resulted in an unacceptable level of endometrial protection. Therefore, we are interested in exploring the effect of intrinsic and extrinsic factors on BZA exposure. It is equally important to make sure that the PK model for Phase III data is adequate. Additionally, it is necessary to investigate dose-response relationship for hyperplasia using adjusted dose as the exposure, given the identified limitation in the sponsor's analysis.

Objectives

Analysis objectives are:

-to evaluate the adequacy of the population PK analysis for the dense data;

-to explore intrinsic and extrinsic factors that may influence BZA PK parameters using population PK model for the dense database;

-to explore dose-response relationship for hyperplasia using combined data from studies 303, 304

Methods

Data Sets

Data sets used are summarized below:

Table 11: Analysis Data Sets

Study Number	Name	Link to EDR
Dense.xpt		\\cdsesub5\EVSPROD\NDA022247\0000\m5\datasets\study-population-pk-108-114-1120-1121-203-300-303-304\analysis

Reference ID: 3319890

Software

The population PK analysis was conducted with NONMEM 6 on a 48-(b) (4) Linux Cluster in a grid environment (Sun Grid Engine 6.2). SAS for Windows 9.3 and R2.15.1 was used for data assembly, statistical analysis, and graphing. Xpose4 and an internally developed population PK tool were used for post-NONMEM analysis.

Models

One compartment model with first-order absorption was used to describe the dense data included in study 108, 1120, 1121, and 114. This is the same as the model used by the sponsor.

Results

Goodness-of-Fit Plots for the Final PK Model for the Dense Data

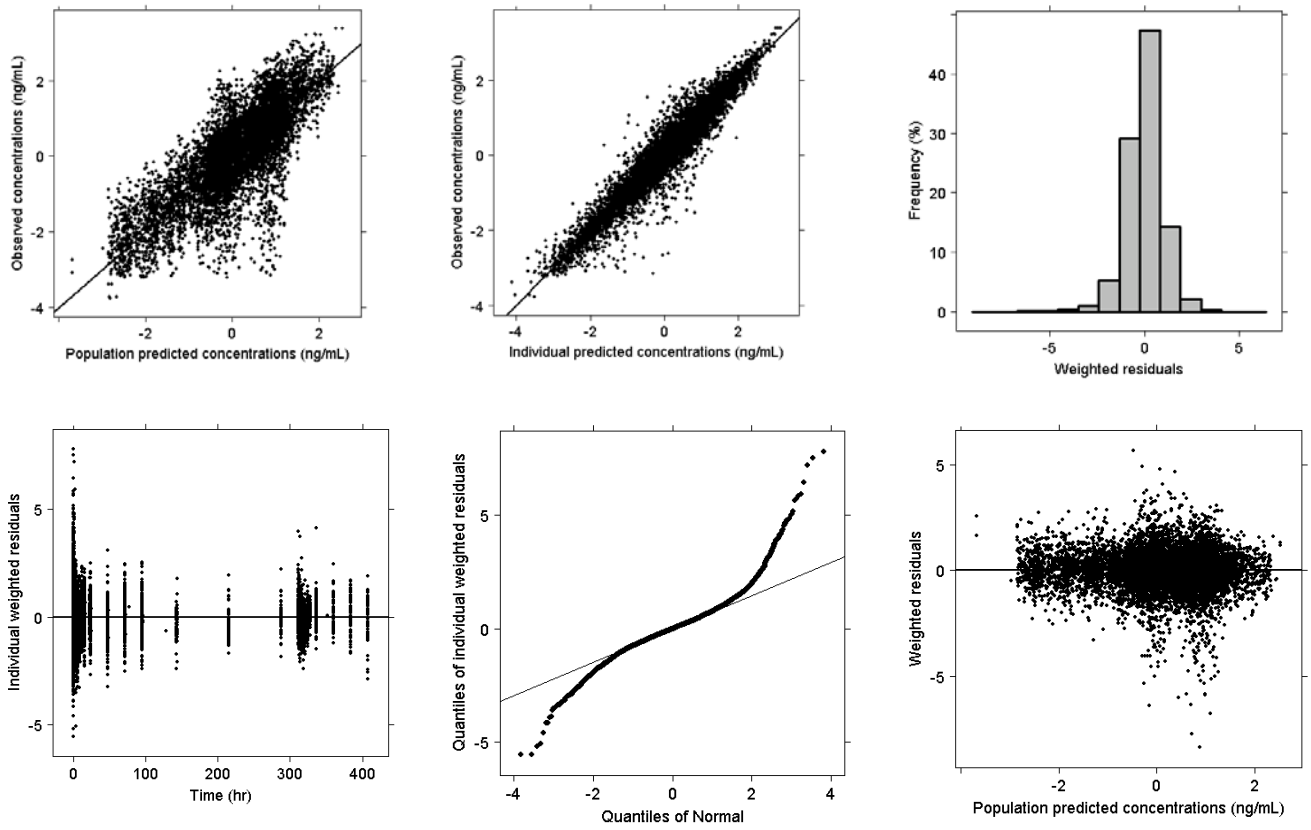


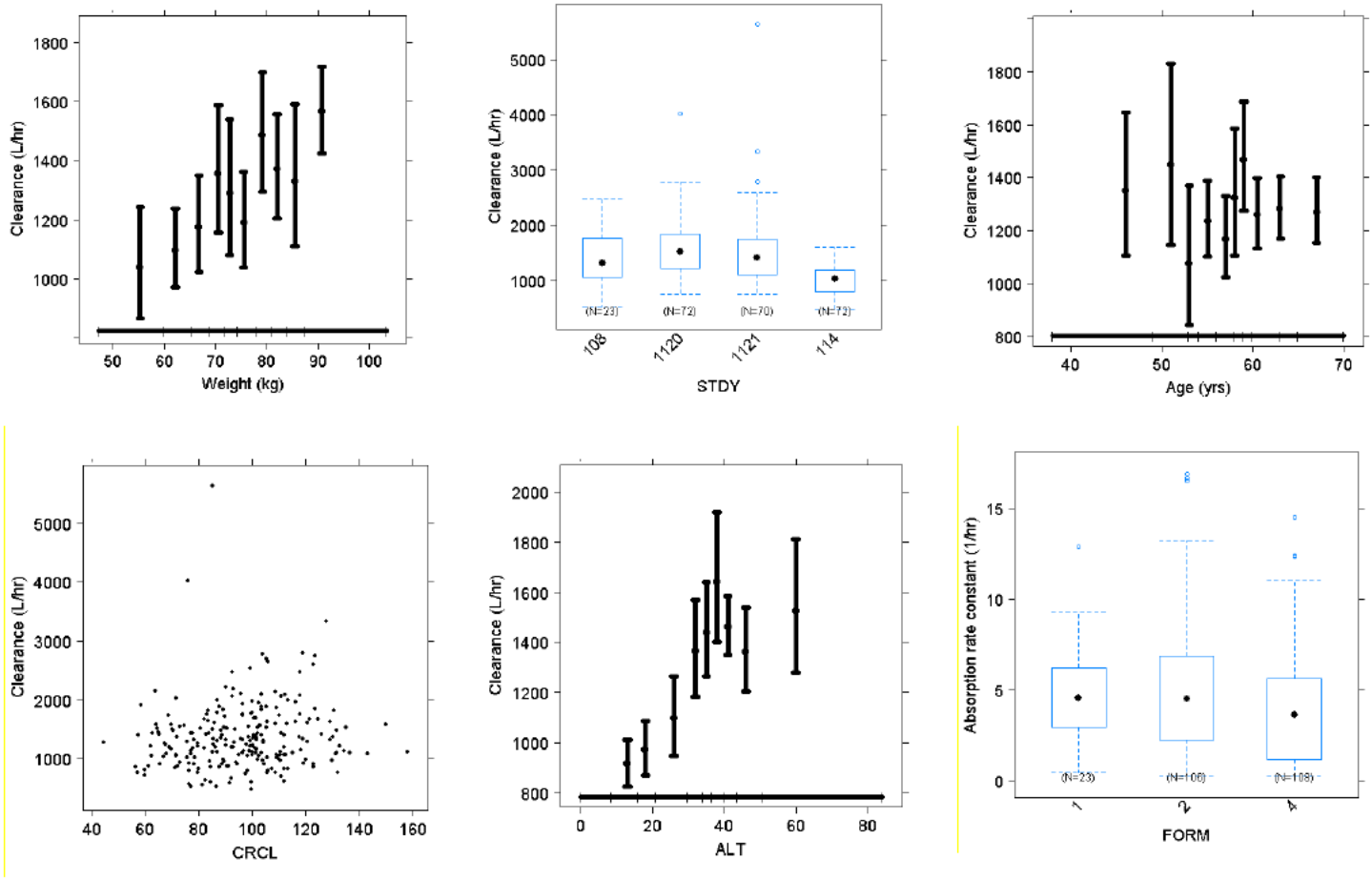
Figure 14: Goodness-of-fit graphs for the final PK model for the Dense Data. Observations vs. population and individual (top center) predictions, weighed residuals vs. time, population predictions, quintiles of standard normal, and a histogram of weighted residuals; The solid black line is the line of unity/identity

Effect of Intrinsic and Extrinsic Factors on PK Parameters of BZA

Relationship between PK parameters and covariates of interest was plotted. Higher body weight and ALT appeared to be associated with larger clearance.

Reference ID: 3319890

Figure 15: Investigated Covariate-PK Parameter Relationships (The box plots and black dots are based on empirical Bayes individual estimates)



Dose-Response Analysis for Endometrial Hyperplasia

The data below summarize the rate of endometrial hyperplasia and its confidence interval after 6, 12, and 24 month of therapy in study 303. The hyperplasia rate is BZA dose- dependent. Higher rate was associated with lower BZA doses.

Reference ID: 3319890

Table 12: Summary of Endometrial Incidence at Month 6, 12 and 24 (Study 303, MITT)

					95% CI (1-sided)		95% CI (2-sided)	
Treatment	Time slot	Number of subjects	Number of hyperplasia	Hyperplasia rate (%)	LL	UL	LL	UL
Placebo	MONTH 6	360	0	0.00	0.00	0.83	0.00	1.02
	MONTH 12	363	0	0.00	0.00	0.82	0.00	1.01
	MONTH 24	363	0	0.00	0.00	0.82	0.00	1.01
Premarin 0.45 mg/TSE-424 10 mg	MONTH 6	363	0	0.00	0.00	0.82	0.00	1.01
	MONTH 12	366	3	0.82	0.22	2.10	0.17	2.38
	MONTH 24	366	8	2.19	1.09	3.91	0.95	4.26
Premarin 0.45 mg/TSE-424 20 mg	MONTH 6	370	0	0.00	0.00	0.81	0.00	0.99
	MONTH 12	373	0	0.00	0.00	0.80	0.00	0.98
	MONTH 24	373	2	0.54	0.10	1.68	0.07	1.92
Premarin 0.45 mg/TSE-424 40 mg	MONTH 6	354	0	0.00	0.00	0.84	0.00	1.04
	MONTH 12	357	0	0.00	0.00	0.84	0.00	1.03
	MONTH 24	358	0	0.00	0.00	0.83	0.00	1.03
Premarin 0.625 mg/TSE-424 10 mg	MONTH 6	(b) (4)						
	MONTH 12							
	MONTH 24							
Premarin 0.625 mg/TSE-424 20 mg	MONTH 6							
	MONTH 12							
	MONTH 24							
Premarin 0.625 mg/TSE-424 40 mg	MONTH 6							
	MONTH 12							
	MONTH 24							
Raloxifene 60 mg	MONTH 6	353	0	0.00	0.00	0.85	0.00	1.04
	MONTH 12	355	0	0.00	0.00	0.84	0.00	1.03
	MONTH 24	355	0	0.00	0.00	0.84	0.00	1.03

Figures below show relationship between the probability of positive endometrial hyperplasia rate and BZA doses after 12 (Figure 16) and 24 months (Figure 17) of BZA/CE treatment. The red dots are observations and the green line and shaded area show model predictions and 95% CI from logistic regression. BZA dose 20 mg in study 304 was corrected by a ratio of 0.7 due to lower bioavailability. The hyperplasia rate was BZA dose -dependent. Higher hyperplasia rate was associated with lower BZA doses.

Figure 16: Probability of positive endometrial hyperplasia after 12 month of treatment with BZA/CE (Combined data from study 303 and 304, EE Population)

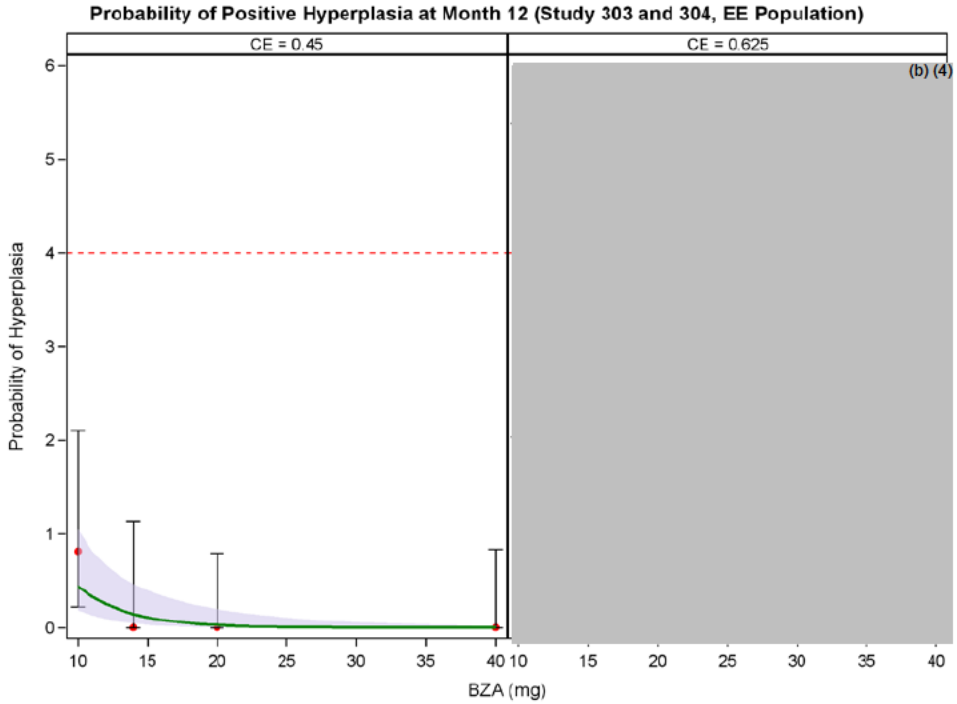
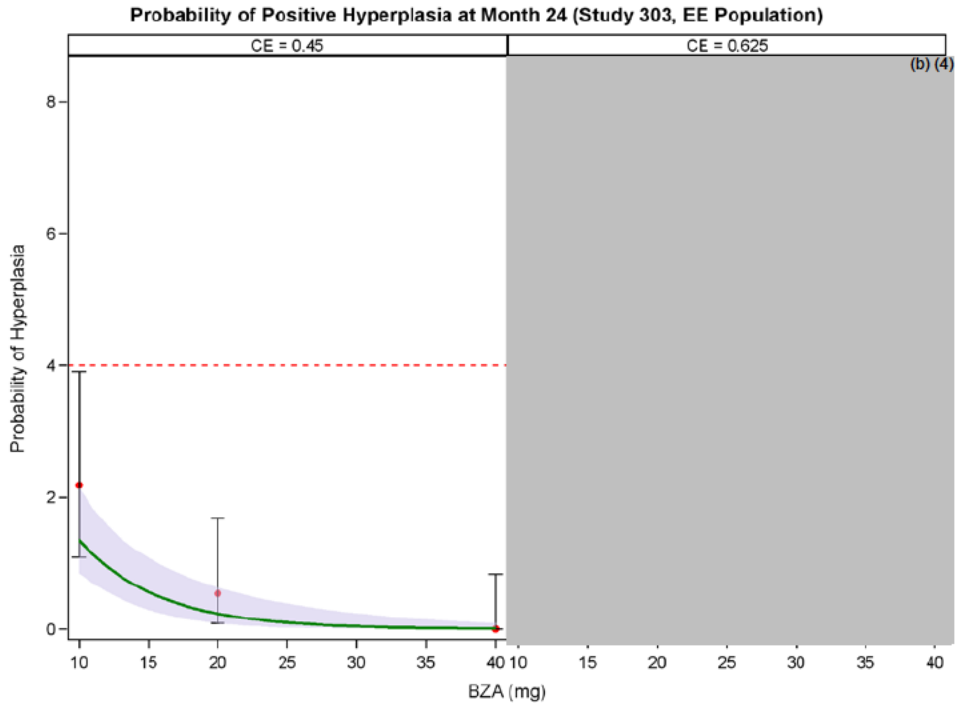


Figure 17: Probability of positive endometrial hyperplasia after 24 month of treatment with BZA/CE (Combined data from study 303, EE Population)



LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
hp_303_304_logit.sas	Logistic analysis for dose-response analysis for hyperplasia (study 303 and 304 combined)	TBD

Reference ID: 3319890

4.4 Filing Memo

FINAL
(December 5, 2012)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	022247	Brand Name	TBD™
OCP Division (I, II, III, IV, V)	III	Generic Name	Bazedoxifene **(BZA)**/ Conjugated estrogens (**CE, Premarin®**)
Medical Division	DRUP	Drug Class	Selective estrogen receptor modulator (SERM) and estrogen receptor agonist
OCP Reviewer	Sayed (Sam,) Al Habet, R.Ph., Ph.D.	Indication (s)	Three indications: Treatment of moderate to severe Vasomotor Symptoms (VMS), moderate to severe symptoms of vulvar and vaginal atrophy (VVA), and prevention of postmenopausal osteoporosis
OCP Secondary Reviewer/Signer	Myong-Jin Kim, Pharm.D.	Dosage Form	20mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE

Reference ID: 3319890

Pharmacometrics Reviewer	Fang Li, Ph.D.	Proposed Dosing Regimen	20mg/0.45mg or 20mg/0.625mg daily
Date of Submission	September 26, 2012 (cover letter) October 3, 2012 (Receipt date)	Route of Administration	Oral
Estimated Due Date of OCP Review	May 2013	Sponsor	Wyeth/Pfizer
Medical Division Due Date	June 2013	Priority Classification	Standard
PDUFA Due Date	October 3, 2013 (***PDUFA 5 Goal Dated***)		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	X	40		
Mass balance:		1		
Isozyme characterization:		1		
Blood/plasma ratio:				
Plasma protein binding:		1		
Pharmacokinetics (e.g., Phase I) -	X	40		
Healthy Volunteers-				
single dose:	X	25		
multiple dose:	X	3		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		2		

Reference ID: 3319890

fasting / non-fasting multiple dose:				
Drug-drug interaction studies		**7**		
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:		1		
renal impairment:				
hepatic impairment:		1		
PD -				
Phase 2:	x			
Phase 3:	x	3		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	2		
Population Analyses -		4		
Data rich:	x	4		
Data sparse:	x	4		
II. Biopharmaceutics		15		
Absolute bioavailability	x	1		
Relative bioavailability -	x	15		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -		15		
traditional design; single / multi dose:	x			
replicate design; single / multi dose:	x			
Food-drug interaction studies	x	2		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	x			
***In vitro* Penetration Studies**				
Genotype/phenotype studies				

Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies		40		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the	X			

Reference ID: 3319890

	pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes_

Executive Filing Summary:

What is the rationale for this Combination Product?

This is a combination of a New Molecular Entity (NME), Bazedoxifene (BZA also known as TSE-424) which is a third generation selective estrogen receptor modulator (SERM) and estrogen receptor agonist, conjugated estrogens (Premarin®). Mechanistically, the combination product is referred to as tissue-selective estrogen complex (TSEC).

BZA and CE function by binding to and activating the two estrogen receptors (α and β). CE is composed of multiple estrogens that demonstrate tissue selective estrogen receptor agonist activity. Bazedoxifene demonstrates both tissue selective estrogen receptor agonist and antagonist activity, exhibiting agonist activity on the skeletal system, while acting as an estrogen antagonist in breast and uterine tissue.

The rationale for the development of BZA/CE is based on the hypothesis that BZA will be acting primarily as an estrogen receptor antagonist in uterine and breast tissue. This will inhibit the proliferative effects of CE on the endometrium and reduce the incidence of uterine bleeding, breast pain/tenderness, and increased breast density associated with existing traditional progestin-containing hormone therapy (HT). CE is expected to effectively relieve menopause related symptoms (e.g., hot flushes, symptoms of VVA, vaginal dryness, and dyspareunia). In addition, in view of the positive effects of CE and BZA on the skeleton, it is expected that the combination of the 2 agents would be effective in the prevention of postmenopausal osteoporosis.

Historical Perspective of BZA:

BZA is approved in Europe, Japan and other countries for the treatment of postmenopausal osteoporosis. (b) (4)

Formulation and Formulation Development:

BZA/CE tablets are a fixed dose combination product (b) (4) The proposed to-be-marketed (TBM) tablet strengths are 20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE.

BZA acetate drug substance is the same as that used in the BZA monotherapy product (b) (4) (b) (4)

The proposed TBM formulations consist of the commercial 0.45 mg or 0.625 mg Premarin® (b) (4)

The sponsor conducted extensive formulation and process development, dissolution development, and **15** biopharmaceutics (bioavailability and bioequivalence) studies including effect of food studies for the development the final proposed TBM BZA/CE drug product (**Appendix 1**). Studies for both the BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg dose strengths are described herein. Furthermore, the sponsor performed in-vitro-in-vivo (IVIVC) analysis.

In addition, the sponsor conducted additional **25** clinical pharmacology studies to characterize the PK of BZA and CE following BZA alone and in combination with CE (**Appendix 2**).

Summary of Formulation Development Studies:

As stated above, 15 bioavailability /bioequivalent studies were conducted to establish the link among several formulations used in Phase I, II and III studies. The following is the definition of important terms used in these studies:

- Premarin current process (**PCP**) formulation: Refers to the formulation used to manufacture Premarin tablets for the US market prior to 2004, which utilized (b) (4) (b) (4)
- Premarin new process (**PNP**) formulations: refers to the formulation used to manufacture Premarin tablets for the US market after 2004, which utilizes (b) (4) **Formulations B, C, and D** (including the proposed TBM formulations) (b) (4)

- **Formulation A:** With a PCP CE (b) (4) that share a similar composition, but differ in the strength of BZA and CE.

- **Formulation B:** With PNP CE (b) (4) and share a similar composition, but differ in the strength of BZA and CE.

- **Formulation C:** (b) (4) change in Formulation B tablets

- **Formulation D:** Formulations that share a similar composition but differ in (b) (4). Formulation D was only used in Phase 1 clinical studies.

Table 1 lists and summarizes the formulations used in relevant studies submitted in this NDA's:

Table 1. Formulations Used in Clinical Pharmacology and Clinical Studies

Formulation	A	B	C	D (Including Proposed TBM)
Type of Study	2-year Phase 3 endometrial safety, BMD, VVA, and VMS study (3115A1-303-US/EU/BR) 1-year Phase 3 endometrial safety and osteoporosis prevention study (3115A1-3307-WW) Food Effect study (3115A1-102-US) Drug Interaction Study (3115A1-101-US) BA/BE Studies (3115A1-100-US, 3115A1-109-US, 3115A1-114-US, 3115A1-1120-US, 3115A1-1121-US, 3115A1-1117-US, 3115A1-1122-US, 3115A1-1137-US, 3115A1-1117-US	2-year Phase 3 endometrial safety and BMD study (3115A1-304-WW) 3-month Phase 3 VMS study (3115A1-305–US) 3-month Phase 3 VVA study (3115A1-306-WW) BA/BE Studies (3115A1-1117-US, 3115A1-1139-US, 3115A1-1142-US IVIVC Study (3115A1-115-US)	Phase 3 Study 3115A1-304-WW Used Formulation C for 8 months of first year and all of second year BA/BE Studies (3115A1-114-US, 3115A1-1120-US, 3115A1-1121-US, 3115A1-1117-US, Food Effect Study (3115A1-1116-US)	Proposed TBM only used in these 4 bioequivalence studies: (3115A1-1122-US, 3115A1-1139-US, 3115A1-1137-US, 3115A1-1142-US) Other studies using Formulation D: BA/BE Study (3115A1-1117-US) Multiple-Dose Study (3115A1-1138-US) BZA Polymorph Study (3115A1-1143-US)
Formulation Description	(b) (4)			

Abbreviations: BMD = bone mineral density; BR = Brazil; CE = conjugated estrogens; EU = European Union; PCP = Premarin current process; PNP = Premarin new process; US = United States; VMS = vasomotor symptoms; VVA = vulvar-vaginal atrophy; WW = world-wide.

Source: Module 2.7.2 P.2.2), Table 3

Sponsor's Conclusions from Bioavailability/Bioequivalent Studies:

Study 3068A1-111-EU (Absolute Bioavailability):

Design: 3 mg IV vs 10 mg PO (BZA alone)
Conclusion: F=6% (absolute bioavailability)

Study 3115A1-102 (Effect of Food):

Design: 40 mg BZA/0.625 CE with or without high fat meal (PCP formulation, Formulation A (formulation used in Phase III studies 303 and 3307)
Conclusion: Increase Cmax (44%) and AUC (17%) with food
Study 3115A1-1116 (Effect of Food):

Design: 20 mg BZA/0.625 CE with or without high fat meal (PNP formulation, **Formulation C**
Conclusion: No change in Cmax, AUC increased by 25% with food

Study 3115A1-114 (PCP vs PNP):

Design: 20 mg BZA/0.625 CE (Formulation A vs Formulation B)
Conclusion: Failed

Study 3115A1-1120 (PCP vs PNP):

Design: 20 mg BZA/0.625 CE (Formulations C vs A), partial replicate design
Conclusion: Failed

Study 3115A1-1121 (PCP vs PNP), steady-state (14 days)

Design: 20 mg BZA/0.625 CE (Formulation A vs Formulation C)
Conclusion: Failed

Study 3115A1-1117 (A, B, C, and PNP): Clinical and commercial

Design: 20 mg BZA/0.625 CE (Formulation A, B, C, D-PCF (**PCF:** potential commercial formulation)
Conclusion:

D vs A failed
D vs B pass
D vs C Pass
B vs A pass
C vs A failed
C vs B pass

Study 3115A1-1122 (3 formulations vs A)

Design: Definitive BE study. (Formulation A vs **TBM, E, F, G**), 20 mg BZA/**0.625** CE
P.S. reformulated (b) (4)
Conclusion: A vs F passed for 20 mg BZA/**0.625** CE strength

Study 3115A1-1139 (B vs TBM)

Design: Definitive BE study. (Formulation B vs **TBM)**, 20 mg BZA/**0.625** CE
Conclusion: B vs F passed for 20 mg BZA/**0.625** CE strength

Study 3115A1-1137 (A vs TBM)

Design: (Formulation A vs **TBM, 1, 2, 3)**, 20 mg BZA/**0.45** CE
Conclusion: A vs TBM 2 passed for 20 mg BZA/**0.45** CE strength

Study 3115A1-1142 (B vs TBM)

Design: (Formulation A vs **TBM, 1, 2, 3)**, 20 mg BZA/**0.45** CE
Conclusion: B vs TBM 1 passed for 20 mg BZA/**0.45** CE strength

Summary of Formulation Bridging Studies;

Based on all BE studies, the following conclusions were made by the sponsor:

- Formulation A≠ C (Study 1120, 1121 and 1117 for 20/0.625mg strength)
- Formulation A= B (Study 1117 for 20/0.625mg strength)
- Formulation B = C (Study 1117 for 20/0.625mg strength)
- Formulation A = TBM (Study 1122 for 20/0.625mg strength)
- Formulation B = TBM (Study 1139 for 20/0.625mg strength)
- Formulation A = TBM (Study 1137 for 20/0.45mg strength)
- Formulation B = TBM (Study 1142 for 20/0.45mg strength)

In the clinical trial 304, patients initially receive formulation B and then switched to formulation C (20/0.45 and 0.625 mg) during the first 8 months of the first year and continued for the second year of the study. (b) (4)

Reviewer's Comments:

The sponsor conducted extensive program to optimize the formulation for this combination product. Many of the studies did not pass the bioequivalence criteria for BZA and/or CE components of the product at either Cmax or AUC levels.

The drug will be administered without regard of food. However, food appears to slightly increase exposure (pending review). The dosage and indications are as follows:

- Moderate to severe vasomotor symptoms: 20/0.45 or 20/0.625 mg QD
- Moderate to severe vaginal atrophy: 20/0.625 mg QD
- Prevention of osteoporosis: 20/0.45 or 20/0.625 mg QD

From the clinical pharmacology perspective, the following are some of the PK info of BZA:

- Half-life: ~30 h
- F= 6%
- Binding: 98-99%
- Excretion: Mainly in bile/feces and 1% in urine (radioactivity)
- Extensively metabolized: 4-fold increase in exposure in patients with hepatic impairment
- Metabolic Pathway: Glucuronidation is the major metabolic pathway
- Not recommended in patients with renal impairment.

Based on the above information and the known safety profiles of BZA, the exposure level will be carefully assessed in this NDA to optimize the chronic therapy with this product. From the clinical pharmacology perspective, there are three major challenges with this NDA as follows:

- Ensuring bridging of all formulations used in this NDA
- Factors that may lower BZA exposure and consistency in absorption. Lowering BZA exposure or reduce absorption may be associated with safety concern due to lack of adequate endometrial protection.
- Factors that may increase BZA exposure are also associated with both safety and efficacy issues. The increase in BZA exposure may reduce CE efficacy (VMS, VVA, and bone mineral density).

Therefore, consistency in BZA absorption, delivery, and systemic exposure appears to be critical in optimizing the long term therapy with this product.

Office of Scientific Investigations (OSI) Inspection:

No OSI inspection is necessary for the analytical and the clinical sites where the PK studies were conducted and blood samples analyzed. The reason for this decision is based on the favorable historical and recent inspections for these sites by OSI.

Comments to Sponsor's for 74-Day:

- Per the meeting minutes (Page 9) held on February 12, 2008, please submit to this NDA the audit report (b) (4) for the BZA/Atorvastatin drug interaction study (study # 3068A1-126-EU).
- Confirm that study # 3068A1-126-EU is the only study that was conducted (b) (4)
- Please provide the list of studies and their audits (if any) that were conducted or analyzed (b) (4)

Recommendation:

The NDA can be filed from the clinical pharmacology perspective.

Sayed (Sam) Al Habet, R.Ph., Ph.D.

Myong-Jin Kim, Pharm.D.
Secondary Reviewer Date

Appendix 1: List of Biopharmaceutics (Bioavailability and Bioequivalence) Studies

Type of Study (Location of CSR) Study Number and CSR Number	Study Objective(s)	Study Design and Type of Control	Test Product[a]; Dose Regimen; Route of Administration	Number of Subjects	Duration of Treatment[b]
Food-Effect Studies					
3115A1-102-US CSR-49949	Assess the effect of a high-fat meal on the relative bioavailability of BZA/CE; safety and tolerability.	Open-label, single-dose, randomized, 2-period crossover study.	BZA 40 mg/CE 0.625 mg fasting and after a high-fat meal. Oral	24	1 day
3115A1-1116-US CSR-69234	Assess the effect of a high-fat meal on the bioavailability of BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized-to-sequence, 3-period, crossover study.	BZA 20 mg/CE (PNP) 0.625 mg fasting or after a high-fat meal. BZA 20 mg/CE (PNP) 0.45 mg fasting. Oral	23	1 day
Comparative Bioavailability and Bioequivalence Studies					
3115A1-100-US CSR-45476	Compare the relative bioavailability of BZA and CE administered as separate tablets or as a combination-tablet formulation.	Open-label, single-dose, 3-treatment, 3-period, randomized crossover study.	BZA 10 mg x 4 and CE 0.625 mg BZA 10 mg/CE 0.625 mg BZA 40 mg/CE 0.625 mg Oral	24	1 day
3115A1-109-US CSR-62706	Assess the comparative bioavailability of 2 new formulations of BZA/CE (PNP) with BZA/CE (PCP) and with CE (PNP).	Open-label, single-dose, 4-period, crossover study.	BZA 40 mg/CE (PNP) 0.625 mg (b) (4) (Formulation B) BZA 40 mg/CE (PNP) 0.625 mg (b) (4) (Formulation B) BZA 40 mg/CE (PCP) 0.625 mg (Formulation A) CE (PNP) 0.625 mg Oral	24	1 day
3115A1-114-US CSR-67989	Assess the bioequivalence of BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized-to-sequence, 2 period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	72	1 day
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1117-US CSR-69737	Assess the bioequivalence of BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized, 4-period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation B) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) BZA 20 mg/CE (PNP) 0.625 mg (Formulation D [PCF]) Oral	76	1 day
3115A1-1120-US CSR-69235	Assess the bioequivalence between BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized, 3-period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	72	1 day

3115A1-1121-US CSR-69445	Assess subject exposure to BZA from 1 of 2 formulations of BZA 20 mg/CE 0.625 mg after steady-state administration.	Open-label, randomized, parallel inpatient/ outpatient study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	36 36	14 days
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1122-US CSR-75506	Assess the bioequivalence of clinical and commercial formulations of BZA/CE combination tablets.	Open-label, single-dose, randomized, 4-period, 4-treatment, crossover, bioequivalence inpatient/outpatient study.	BZA 20 mg/CE 0.625 mg (Formulation A - reference therapy). BZA 20 mg/CE 0.625 mg (Potential commercial formulation E - test formulation). BZA 20 mg/CE 625 mg (Potential commercial formulation F - test formulation). BZA 20 mg/CE 0.625 mg (Potential commercial formulation G – test formulation). Oral	82	1 day
3115A1-1137-US CSR-77978	Bioequivalence of test and reference formulations of BZA/CE combination tablets, assessing both the BZA and CE components.	Open-label, single-dose, randomized, 4-period, 4-treatment, crossover study.	BZA 20 mg/CE 0.45 mg (Formulation A-reference therapy) BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). Oral	90	1 day
3115A1-1139-US CSR-76333	Assess the bioequivalence of clinical and commercial formulations of BZA/CE combination tablets, assessing both the BZA and CE components.	Open-label, single-dose, randomized, 2-period, 2-treatment, crossover study.	BZA 20 mg/CE 0.625 mg (Formulation B - reference therapy). BZA 20 mg/CE 0.625 mg (proposed TBM formulation - test formulation). Oral	90	1 day
In Vitro/In Vivo Correlation Studies					
3115A1-115-US CSR-68097	Assess the bioavailability of BZA (b) (4) formulations of BZA/CE and an oral solution of BZA.	Open-label, single-dose, randomized, crossover study.	BZA 20 mg/CE 0.625 mg with the BZA component being: (b) (4) BZA 20 mg powder for oral solution Oral	24	1 day
3115A1-1123-US CSR-72948	Bioavailability of BZA/CE.	Open-label, single-dose, nonrandomized, 4-period, crossover study.	(b) (4) BZA 20 mg/CE 0.625 mg (b) (4) BZA 20 mg/CE 0.625 mg (b) (4) BZA 20 mg/CE 0.625 mg BZA 20 mg (oral solution) Oral	28	1 day

3115A1-1142-US CSR-78945	Assess the bioequivalence of 4 formulations of BZA/CE.	Open-label, single-dose, randomized, 4-period, crossover study.	BZA 20 mg/CE 0.45 mg (Formulation B – reference formulation). BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). Oral	88	1 day
3115A1-1143-US CSR-77979	Assess the bioavailability of 3 test formulations of BZA/CE (b) (4) (b) (4) compared with a potential market (reference) formulation of BZA/CE combination tablets, assessing only the BZA component.	Open-label, single-dose, randomized, 4-period, 4-treatment crossover study.	BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). BZA 20 mg/CE 0.45 mg (PCF - reference therapy) Oral	37	1 day

Abbreviation: BZA=bazedoxifene; CE=conjugated estrogens; CSR=clinical study report; EU=European Union; IV=intravenous, PK=pharmacokinetics; PCP = Premarin current process; PNP = Premarin new process.

a. All test products were tablets unless otherwise specified.

b. Duration of treatment is the per protocol number of units of time (days, weeks, months, years) that individual subjects were exposed to the test article(s).

Source: Compounds (b) (4) Regulatory and Summaries/Summaries/Supporting Information/Bazedoxifene Conjugated Estrogens 2011 Table of all Clinical Studies

Appendix 2: List of Clinical Pharmacology Studies

Initial Safety, PK and PD	Drug Interactions	Drug Interactions	Exposure Response	ADME Biodistribution	Special Populations
SAD (3068A1-100-US)	Drug Interaction - Antacid (3068A1-102 FR)	**Drug Interaction-BZA/CE (3115A1-101-US)**	Population PK (3068A1-203-GL)	BZA ADME ^{14}C Radiolabel (3068A1-103-US)	Hepatic Disease (3068A1-112-EU)
MAD (3068A1-101-US)	Drug Interaction - Ibuprofen - (3068A1-106-SP)	**Drug Interaction-BZA on CE (3115A1-1134-US)**	Population PK (3068A1-300-GL)	BZA Absolute Bioavailability (3068A1-111-EU)	Age/Renal (3068A1-121-US)
BZA/CE Multiple Dose (3115A1-1138-US)	Drug Interaction - Azithromycin - (3068A1-125-EU)	**Drug Interaction-CE on BZA (3115A1-1135-US)**	QTc Study (3068A1-131-US)	BZA Dose Proportionality (3068A1-108-US)	SAD in China (3068A1-123-CI)
	Drug Interaction - Atorvastatin - (3068A1-126-EU)		Population PK (3115A1-303-US)	**BZA – BZA/CE Relative Bioavailability (3115A1-1136-US)**	SAD in Japan (3068A1-114-JA)
			Population PK (3115A1-304-WW)		MAD in Japan (3068A1-124-JA)

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; BZA = bazedoxifene; CE = conjugated estrogens; EU = Europe; FR = France; GL = global; JA = Japan; MAD = multiple ascending dose; PD = Pharmacodynamic; PK = Pharmacokinetic; QT_c = interval between the Q-wave and T-wave of the electrocardiogram, corrected; SAD = single ascending dose; US = United States; WW = worldwide

Note: Studies with the prefix 3068A1 were conducted with bazedoxifene monotherapy; studies with the prefix 3115A1 were conducted using BZA/CE. The studies conducted specifically for the BZA/CE development program are shown in bold font.

a. Four (4) studies listed in this figure were Phase 2 (3068A1-203-GL) or Phase 3 (3068A1-300-GL, 3115A1-303-US, and 3115A1-304-WW) studies that were used for population PK analyses.

Reference ID: 3319890

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAYED AL HABET
06/05/2013

LAI M LEE
06/05/2013

FANG LI
06/05/2013

YANING WANG
06/05/2013
Signing for the Pharmacometrics component.

MYONG JIN KIM
06/05/2013

EDWARD D BASHAW
06/05/2013
This NDA has several unresolved formulation identity issues as of June 5th, 2013. The reader is strongly advised to review pages 64-74 of the attached review first, as these issues and there resolution from a pending IR request impact the clinical studies data and their acceptability.

Individual Study Review
Clinical Pharmacology Review
Office of Clinical Pharmacology

NDA: 022247 Date of Submission:	September 26, 2012 (cover letter) October 3, 2012 (receipt date)
Generic Name:	Bazedoxifene (BZA)/Conjugated Estrogens (CE, Premarin®)
Proposed Brand Name:	TBD
Formulation:	Tablet
Strengths:	20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE
Route of Administration:	Oral
Indications:	• Treatment of moderate to severe Vasomotor Symptoms (VMS) • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) • Prevention of postmenopausal osteoporosis (PMO)
Dosage and Administration:	For VMS: BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg QD For VVA: BZA 20 mg/CE 0.625 QD For PMO: BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg QD
Type of Submission:	Original NDA (New Molecular Entity, NME)
Sponsor:	Wyeth/Pfizer
OCP Division:	Division of Clinical Pharmacology 3
Office of New Drugs (OND) Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Primary Clinical Pharmacology Reviewers:	Sayed (Sam) Al Habet, RPh, PhD LaiMing Lee, PhD
Clinical Pharmacology Team Leader:	Myong-Jin Kim, Pharm.D.
Primary Pharmacometric Reviewer:	Fang Li, Ph.D.
Pharmacometric Team Leader:	Yaning Wang, Ph.D.
Division Director:	E. Dennis Bashaw, Pharm.D.

Reference ID: 3319979

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4.2. Individual Study Review (Selected Studies)

A. **Biopharmaceutics Studies**:

The sponsor conducted BE studies to establish the link between several formulations that were developed over the years during the drug development. The focus of the review is on the BZA data as most of the studies have demonstrated BE for the CE. However, the 90% CIs for the BZA components of the products failed to meet the BE limits of 80% to 125% in most of the studies. The detail information about each formulation is discussed in the biopharmaceutics section of this review.

Study 1117-US (Pivotal, Clinical "A, B, C" and Commercial Formulations "D"):

Title: "An Open-label, Single-Dose, Randomized, 4-Period, Crossover, Bioequivalence Study of Clinical and Commercial Formulations of Bazedoxifene/Conjugated Estrogens in Healthy Postmenopausal Women"

Objectives: The primary objective of the study was to assess the BE of formulations used in clinical studies and a potential commercial formulation of BZA/CE combination tablets, assessing the BZA and CE components.

Rationale:

The purpose of this study was to establish the relationship of BZA and CE exposures of the 3 formulations used in the phase 3 clinical studies to those of a potential commercial formulation.

Design:

This was a single-dose, randomized, open-label, 4-period, 4-treatment, crossover, BE study in 75 healthy inpatient/outpatient postmenopausal subjects with a 10-day washout period. Each subject received a single dose of each formulation after an overnight fast of at least 10 hours until 4 hours after drug administration. Subjects were randomly assigned to 1 of 4 sequences: A/B/C/D, B/D/A/C, C/A/D/B, or D/C/B/A for the following 4 treatments:

Treatment A: Clinical Formulation A
Treatment B: Clinical Formulation B
Treatment C: Clinical Formulation C
Treatment D: Potential Commercial Formulation D.

The formulations tested in this study are listed in **Table 1117-1**.

Formulation A: (b) (4) it was used in the first safety and efficacy study (3115A1-303-WW).

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Formulations B and C: [redacted] (b) (4) These formulations were used in three pivotal safety and efficacy studies (3115A1-304-WW, 305-WW, and 306-WW).

Table 1117-1. Formulations Tested in Study 1117-US:

Test Article	Dosage Form	Strength	Formulation (Stock) Number	Batch Number
Clin Form A BZA/CE	Film Coated Tablet	20 mg/0.625 mg	0931462C[a]	2003B0239
Clin Form B BZA/CE	Film Coated Tablet	20 mg/0.625 mg	0932162C[b]	115453C
Clin Form C BZA/CE	Film Coated Tablet	20 mg/0.625 mg	0932315C[c]	P6201
P Comm Form D BZA/CE	Film Coated Tablet	20 mg/0.625 mg	0932558C	C43766

Abbreviations: Clin Form = Clinical Formulation; P Comm Form = Potential Commercial Formulation;

Blood Samples:

Blood samples for PK analysis were collected at adequate intervals over 72 hours.

Results:

Unconjugated Estrone:

The mean PK parameters for unconjugated estrone are shown in **Table 1117-2**.

The 90% CIs for Cmax and AUC were within the range of 80% to 125% for almost all comparisons (**Table 1117-3**). The mean PK data and 90% CI for baseline corrected unconjugated estrone are shown in **Tables 1117-4 and 1117-5.**

Table 1117-2. Mean PK Parameters for unconjugated Estrone (Study 1117-US)

Treatment		C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	60.9 ± 21.8	11.3 ± 6.0	56.1 ± 24.0	2572 ± 921	4790 ± 2564
	%CV	35.8	53.2	42.7	35.8	53.5
	N	76	76	76	76	76
	Geometric Mean	57.1	10.1	51.7	2420	4262
	(Range)	(19.7-125)	(4.5-32.0)	(19.0-145)	(968-6224)	(1477-16289)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	57.2 ± 19.2	10.1 ± 5.9	61.7 ± 49.3	2502 ± 911	4809 ± 2916
	%CV	33.6	58.8	79.9	36.4	60.6
	N	76	76	76	76	76
	Geometric Mean	54.2	8.9	54.9	2347	4245
	(Range)	(18.6-130)	(3.0-32.0)	(23.2-448)	(865-6429)	(1481-22718)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	57.8 ± 21.1	10.3 ± 6.8	60.5 ± 50.7	2460 ± 859	4540 ± 2007
	%CV	36.5	66.1	83.7	34.9	44.2
	N	75	75	75	75	75
	Geometric Mean	54.2	8.9	53.8	2303	4105
	(Range)	(19.1-131)	(3.0-48.0)	(25.1-461)	(936-4661)	(1330-10142)
1 BZA 20 mg/ CE 0.625 mg Tablet (Potential Commercial Formulation D)	Mean ± SD	59.1 ± 20.8	10.2 ± 4.9	55.5 ± 25.4	2492 ± 784	4457 ± 1711
	%CV	35.1	48.0	45.8	31.5	38.4
	N	76	76	76	76	76
	Geometric Mean	55.9	9.3	51.6	2363	4123
	(Range)	(24.9-127)	(4.5-24.0)	(22.2-216)	(1035-4372)	(1352-9927)

Abbreviations: C_{max} = peak concentration; t_{max} = time to peak concentration; $t_{½}$ = terminal-phase elimination half-life; AUC_T = area under the concentration-time curve to the last measurable concentration at time T; AUC = total area under the concentration-time curve.

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Table 1117-3. The 90% CI for PK Parameters for unconjugated Estrone (Study 1117-US)

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.950	.797	.865	.857	.841
Treatment	.175	.083	.335	.039	.681
Period	.809	.053	.386	.364	.216
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]					
Statistical Power (%)	100.0	96.9	-	100.0	100.0
GLS Mean Ratio	95	88	-	97	100
90% C.I.	91-99	80-97	-	95-99	94-105
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	95.8	-	100.0	100.0
GLS Mean Ratio	95	88	-	96	97
90% C.I.	91-100	80-98	-	93-99	91-103
Clinical Formulation A (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	98.3	-	100.0	100.0
GLS Mean Ratio	98	92	-	98	97
90% C.I.	93-103	84-101	-	95-101	92-102
Clinical Formulation B (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	92.5	-	100.0	100.0
GLS Mean Ratio	100	101	-	99	97
90% C.I.	97-104	90-112	-	95-102	91-104
Clinical Formulation B (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	96.2	-	100.0	100.0
GLS Mean Ratio	103	105	-	101	97
90% C.I.	99-107	95-115	-	98-103	93-102
Clinical Formulation C (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	88.0	-	100.0	100.0
GLS Mean Ratio	103	104	-	102	100
90% C.I.	98-107	93-117	-	100-105	95-105

Table 1117-4. Unconjugated Estrone Adjusted for Baseline:

Treatment		C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	38.5 ± 20.0	11.3 ± 6.0	16.8 ± 7.8	982 ± 507	1132 ± 605
	%CV	52.1	53.2	46.2	51.6	53.5
	N	76	76	75	76	75
	Geometric Mean	33.2	10.1	15.0	803	941
	(Range)	(3.5-107)	(4.5-32.0)	(2.5-44.3)	(41-2384)	(75-3231)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	34.5 ± 15.8	10.1 ± 5.9	17.2 ± 11.8	895 ± 494	1045 ± 573
	%CV	45.9	58.8	68.9	55.2	54.8
	N	76	76	75	76	75
	Geometric Mean	30.6	8.9	14.8	718	863
	(Range)	(2.6-97.1)	(3.0-32.0)	(2.4-100)	(22-2136)	(35-2904)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	35.9 ± 19.1	10.3 ± 6.8	16.7 ± 8.3	912 ± 521	1065 ± 595
	%CV	53.2	66.1	49.5	57.1	55.9
	N	75	75	73	75	73
	Geometric Mean	31.3	8.9	14.8	725	870
	(Range)	(6.0-115)	(3.0-48.0)	(2.4-46.4)	(49-2147)	(69-2487)

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Treatment		C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
1 BZA 20 mg/	Mean ± SD	37.5 ± 19.7	10.2 ± 4.9	16.2 ± 6.5	932 ± 480	1057 ± 543
CE 0.625 mg	%CV	52.6	48.0	40.1	51.5	51.4
Tablet	N	76	76	75	76	75
(Potential	Geometric Mean	33.2	9.3	14.8	800	910
Commercial	(Range)	(13.1-114)	(4.5-24.0)	(2.5-35.8)	(128-2380)	(140-2595)
Formulation D)						

Table 1117-5. 90% CI of Unconjugated Estrone Adjusted for Baseline:

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.981	.797	.704	.771	.767
Treatment	.295	.083	.990	.161	.335
Period	.311	.053	.153	.006	.018
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]					
Statistical Power (%)	95.0	96.9	-	82.5	96.9
GLS Mean Ratio	92	88	-	89	93
90% C.I.	83-102	80-97	-	79-101	85-103
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	99.7	95.8	-	97.0	94.5
GLS Mean Ratio	95	88	-	91	92
90% C.I.	88-102	80-98	-	83-100	83-102
Clinical Formulation A (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	99.0	98.3	-	95.6	93.9
GLS Mean Ratio	100	92	-	100	98
90% C.I.	92-109	84-101	-	90-110	88-109
Clinical Formulation B (Reference) Versus Clinical Formulation C(Test)[a]					
Statistical Power (%)	99.8	92.5	-	91.3	91.2
GLS Mean Ratio	103	101	-	102	98
90% C.I.	95-111	90-112	-	91-114	88-110

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
Clinical Formulation B (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	99.8	96.2	-	92.8	97.9
GLS Mean Ratio	109	105	-	111	105
90% C.I.	101-117	95-115	-	100-124	95-115
Clinical Formulation C (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	99.7	88.0	-	97.9	97.5
GLS Mean Ratio	106	104	-	110	106
90% C.I.	98-114	93-117	-	100-120	97-117

Reference ID: 3319979

Unconjugated Equilin:

The mean PK parameters for unconjugated equilin are shown in **Table 1117-6**.

The 90% CIs for Cmax and AUCt were within the range of 80% to 125% for all comparisons, except for AUCt for formulation A and C (**Table 1117-7**).

Table 1117-6. Mean PK Parameters for Unconjugated Equilin

Treatment		C_{max} (pg/mL)	t_{max} (h)	AUC_T (pg·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	22.9 ± 12.9	8.6 ± 5.2	279 ± 216
	%CV	56.2	60.4	77.4
	N	76	76	71
	Geometric Mean	22.4	8.5	203
	(Range)	(0.0-76.2)	(0.0-40.0)	(8-1121)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	21.0 ± 10.5	7.7 ± 3.9	280 ± 249
	%CV	50.2	51.0	88.9
	N	76	76	71
	Geometric Mean	20.9	7.7	184
	(Range)	(0.0-70.5)	(0.0-24.0)	(8-1307)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	21.2 ± 12.4	8.0 ± 4.2	264 ± 219
	%CV	58.6	52.6	82.9
	N	75	75	70
	Geometric Mean	20.6	7.9	164
	(Range)	(0.0-77.1)	(0.0-24.0)	(8-1012)
1 BZA 20 mg/ CE 0.625 mg Tablet (Potential Commercial Formulation D)	Mean ± SD	21.9 ± 14.1	7.5 ± 4.0	295 ± 229
	%CV	64.3	53.9	77.7
	N	76	76	68
	Geometric Mean	22.1	7.9	214
	(Range)	(0.0-85.2)	(0.0-24.0)	(8-1095)

Table 1117-7. 90% CI of Unconjugated Equilin:

Treatment	C_{max}	t_{max}	AUC_T
p-Values of Fixed-Effects from Mixed Effects Model of Log-Transformed Pharmacokinetic Parameters			
Source of Variation			
Sequence	.697	.233	.330
Treatment	.118	.199	.039
Period	.593	.707	.228
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval			
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]			
Statistical Power (%)	100.0	99.0	92.2
GLS Means Ratio	94	90	89
90% C.I.	88-99	83-98	80-100
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]			
Statistical Power (%)	100.0	99.4	70.5
GLS Means Ratio	92	94	79
90% C.I.	86-97	87-102	69-92
Clinical Formulation A (Reference) Versus Commercial Formulation D (Test)[a]			
Statistical Power (%)	100.0	95.3	90.0
GLS Means Ratio	96	92	96
90% C.I.	91-101	83-102	86-107
Clinical Formulation B (Reference) Versus Clinical Formulation C (Test)[a]			
Statistical Power (%)	100.0	98.7	65.8
GLS Means Ratio	98	105	89
90% C.I.	93-103	96-114	76-104
Clinical Formulation B (Reference) Versus Commercial Formulation D (Test)[a]			
Statistical Power (%)	100.0	93.9	81.9
GLS Means Ratio	102	102	107
90% C.I.	97-108	92-114	94-122
Clinical Formulation C (Reference) Versus Commercial Formulation D (Test)[a]			
Statistical Power (%)	100.0	95.6	77.3
GLS Means Ratio	104	98	121
90% C.I.	99-111	89-108	106-138

Reference ID: 3319979

Unconjugated Total Estrone:

The mean PK parameters for total estrone are shown in **Table 1117-8**. The 90% CIs for Cmax and AUC were within the range of 80% to 125% for all comparisons, (**Table 1117-9**). The mean PK parameters and 90% CI for baseline corrected total estrone are shown in **Tables 1117-10 and 1117-11.**

Table 1117-8. Mean PK Parameters of Total Estrone:

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	1.98 ± 0.93	8.8 ± 4.0	24.9 ± 6.6	47.6 ± 23.8	59.0 ± 33.7
	%CV	47.0	45.2	26.5	50.0	57.2
	N	76	76	76	76	76
	Geometric Mean	1.77	8.2	24.1	42.2	51.2
	(Range)	(0.23-6.09)	(4.5-24.0)	(10.6-47.9)	(5.8-138)	(7.7-195)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	1.73 ± 0.68	8.1 ± 3.2	26.0 ± 7.6	45.1 ± 22.9	56.1 ± 32.1
	%CV	39.6	39.6	29.2	50.7	57.2
	N	76	76	76	76	76
	Geometric Mean	1.59	7.5	24.9	39.8	48.5
	(Range)	(0.27-4.44)	(3.0-24.0)	(9.4-51.7)	(6.3-131)	(8.8-200)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	1.75 ± 0.86	8.4 ± 3.9	26.1 ± 7.7	45.3 ± 23.8	56.4 ± 32.9
	%CV	49.1	47.2	29.6	52.5	58.3
	N	75	75	75	75	75
	Geometric Mean	1.57	7.7	25.0	39.7	48.4
	(Range)	(0.35-4.32)	(4.5-24.0)	(9.8-48.5)	(6.4-123)	(7.9-172)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Potential Commercial Formulation D)	Mean ± SD	1.79 ± 0.79	8.0 ± 2.8	25.3 ± 7.0	45.7 ± 23.1	56.2 ± 31.3
	%CV	44.0	34.9	27.5	50.6	55.7
	N	76	76	76	76	76
	Geometric Mean	1.62	7.5	24.4	40.5	49.0
	(Range)	(0.37-4.23)	(4.5-16.0)	(10.2-43.6)	(9.5-140)	(11.0-197)

Table 1117-9. 90% CI of Total Estrone:

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.801	.672	.741	.695	.669
Treatment	.013	.237	.516	.046	.058
Period	.768	.236	.767	.116	.208
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]					
Statistical Power (%)	100.0	99.9	-	100.0	100.0
GLS Mean Ratio	90	92	-	94	95
90% C.I.	84-96	86-99	-	90-98	91-98
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	97.8	-	100.0	100.0
GLS Mean Ratio	89	95	-	95	95
90% C.I.	84-94	86-104	-	91-98	92-99
Clinical Formulation A (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.2	-	100.0	100.0
GLS Mean Ratio	92	92	-	96	96
90% C.I.	87-98	85-100	-	92-100	92-99
Clinical Formulation B (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	99.9	-	100.0	100.0
GLS Mean Ratio	99	103	-	100	100
90% C.I.	94-104	95-111	-	96-105	96-105
Clinical Formulation B (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.4	-	100.0	100.0
GLS Mean Ratio	102	100	-	102	101
90% C.I.	97-108	92-109	-	98-106	97-105

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
Clinical Formulation C (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.0	-	100.0	100.0
GLS Mean Ratio	104	97	-	102	101
90% C.I.	99-109	89-106	-	98-105	97-104

Reference ID: 3319979

Table 1117-10. Mean PK Parameters of Baseline Adjusted Total Estrone:

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	1.79 ± 0.88	8.8 ± 4.0	14.6 ± 6.0	33.7 ± 16.1	36.5 ± 18.4
	%CV	49.0	45.2	41.0	47.9	50.5
	N	76	76	76	76	76
	Geometric Mean (Range)	1.58 (0.20-5.90)	8.2 (4.5-24.0)	13.7 (6.7-44.6)	29.9 (3.5-94.7)	32.2 (3.7-112)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	1.53 ± 0.61	8.1 ± 3.2	14.4 ± 4.8	31.1 ± 16.5	33.5 ± 18.9
	%CV	39.8	39.6	33.0	53.1	56.6
	N	76	76	76	76	76
	Geometric Mean (Range)	1.40 (0.22-3.89)	7.5 (3.0-24.0)	13.6 (4.8-28.0)	26.8 (2.4-91.5)	28.6 (3.0-112)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	1.57 ± 0.81	8.4 ± 3.9	14.7 ± 5.8	32.1 ± 18.2	35.0 ± 21.0
	%CV	51.2	47.2	39.6	56.6	59.9
	N	75	75	75	75	75
	Geometric Mean (Range)	1.39 (0.32-4.12)	7.7 (4.5-24.0)	13.7 (5.0-39.6)	27.2 (4.1-91.7)	29.3 (4.6-108)
1 BZA 20 mg/ CE 0.625 mg Tablet (Potential Commercial Formulation D)	Mean ± SD	1.61 ± 0.72	8.0 ± 2.8	14.5 ± 4.8	32.4 ± 16.4	34.8 ± 18.3
	%CV	45.1	34.9	33.3	50.6	52.6
	N	76	76	76	76	76
	Geometric Mean (Range)	1.45 (0.34-4.07)	7.5 (4.5-16.0)	13.8 (4.1-32.3)	28.5 (6.3-98.6)	30.4 (7.0-116)

Table 1117-11. 90% CI Baseline Adjusted Total Estrone:

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.729	.672	.839	.677	.600
Treatment	.027	.237	.967	.041	.023
Period	.697	.236	.442	.058	.038
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]					
Statistical Power (%)	99.9	99.9	-	100.0	100.0
GLS Mean Ratio	89	92	-	90	89
90% C.I.	83-96	86-99	-	84-96	83-95
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	97.8	-	100.0	100.0
GLS Mean Ratio	88	95	-	91	91
90% C.I.	82-95	86-104	-	86-97	86-97
Clinical Formulation A (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	99.9	99.2	-	100.0	100.0
GLS Mean Ratio	92	92	-	95	94
90% C.I.	86-99	85-100	-	90-102	89-100
Clinical Formulation B (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	99.9	-	100.0	100.0
GLS Mean Ratio	99	103	-	102	103
90% C.I.	94-105	95-111	-	95-109	96-110
Clinical Formulation B (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.4	-	99.9	100.0
GLS Mean Ratio	104	100	-	106	106
90% C.I.	97-110	92-109	-	99-114	99-114
Clinical Formulation C (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.0	-	99.8	99.9
GLS Mean Ratio	104	97	-	104	103
90% C.I.	99-110	89-106	-	97-112	96-111

Reference ID: 3319979

Total Equilin:

The mean PK parameters for total equilin are shown in **Table 1117-12**. The 90% CIs for Cmax and AUC were within the range of 80% to 125% for all comparisons (**Table 1117-13**).

Table 1117-12. Mean PK Parameters of Total Equilin (Study 1117)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	1.41 ± 0.87	6.9 ± 2.9	12.0 ± 4.5	21.7 ± 15.3	23.6 ± 17.4
	%CV	61.5	42.7	38.0	70.7	73.9
	N	76	76	76	76	76
	Geometric Mean (Range)	1.20 (0.16-5.90)	6.5 (3.0-24.0)	11.1 (4.3-27.2)	17.4 (1.1-104)	19.2 (1.6-128)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	1.29 ± 0.59	5.6 ± 2.1	12.1 ± 4.9	21.6 ± 15.4	23.6 ± 17.3
	%CV	45.7	37.4	40.5	71.3	73.0
	N	76	76	76	76	76
	Geometric Mean (Range)	1.17 (0.26-3.40)	5.3 (3.0-16.0)	11.2 (4.0-27.6)	17.6 (2.9-98.1)	19.4 (3.7-119)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	1.35 ± 0.75	6.0 ± 2.5	12.0 ± 4.5	21.9 ± 15.2	23.7 ± 17.2
	%CV	56.1	42.1	37.6	69.5	72.2
	N	75	75	75	75	75
	Geometric Mean (Range)	1.17 (0.19-4.36)	5.6 (3.0-16.0)	11.3 (4.3-30.0)	17.6 (2.0-88.1)	19.3 (3.3-112)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Potential Commercial Formulation D)	Mean ± SD	1.38 ± 0.76	6.0 ± 2.5	11.8 ± 3.6	22.3 ± 15.8	24.2 ± 17.8
	%CV	55.6	42.4	30.8	70.8	73.4
	N	76	76	76	76	76
	Geometric Mean (Range)	1.21 (0.37-4.51)	5.6 (3.0-16.0)	11.3 (4.6-25.8)	18.2 (2.3-102)	19.9 (2.8-126)

Reference ID: 3319979

Table 1117-13. 90% CI for Total Equilin (Study 1117)

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.730	.402	.191	.983	.972
Treatment	.632	.010	.967	.753	.850
Period	.329	.578	.101	.697	.519
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]					
Statistical Power (%)	99.8	96.8	-	99.9	100.0
GLS Mean Ratio	97	82	-	101	101
90% C.I.	90-105	75-90	-	94-109	94-108
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	99.9	98.5	-	100.0	100.0
GLS Mean Ratio	97	86	-	101	101
90% C.I.	90-104	79-94	-	95-108	96-106
Clinical Formulation A (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	99.4	97.3	-	99.6	99.9
GLS Mean Ratio	101	87	-	105	104
90% C.I.	93-109	79-95	-	97-113	96-111
Clinical Formulation B (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	100.0	99.9	-	100.0	100.0
GLS Mean Ratio	99	104	-	100	100
90% C.I.	94-105	97-112	-	95-106	95-105
Treatment	**C_{max}**	**t_{max}**	**$t_{½}$**	**AUC_T**	**AUC**
Clinical Formulation B (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.2	-	100.0	100.0
GLS Mean Ratio	103	105	-	104	102
90% C.I.	97-109	97-114	-	97-110	97-109
Clinical Formulation C (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	100.0	99.1	-	100.0	100.0
GLS Mean Ratio	104	101	-	103	103
90% C.I.	98-110	93-110	-	97-110	97-109

BZA:

Previous studies (114-US, 1120-US, and 1121-US) have shown that, for BZA, Formulations A and C are not BE. This study again confirmed that result, and also showed that Formulation A and Formulation D (a potential to-be-market formulation not used in any previous clinical studies) are not BE.

However, Formulation B was BE to all the other formulations, and Formulation C was BE Formulations B and D.

Reference ID: 3319979

Table 1117-16. Geometric Mean PK Parameters for BZA (Study 1117)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation A)	Mean ± SD	4.00 ± 2.15	1.8 ± 2.2	28.1 ± 9.4	52.7 ± 24.9	59.1 ± 29.4
	%CV	53.9	126	33.4	47.3	49.7
	N	76	76	76	76	76
	Geometric Mean (Range)	3.44 (1.04-9.52)	1.3 (0.8-16.0)	26.8 (15.0-60.3)	47.6 (20.7-134)	53.0 (21.7-161)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation B)	Mean ± SD	3.84 ± 2.37	1.5 ± 1.5	29.1 ± 12.4	48.2 ± 27.6	54.2 ± 32.4
	%CV	61.6	102	42.7	57.3	59.8
	N	76	76	76	76	76
	Geometric Mean (Range)	3.09 (0.50-9.69)	1.2 (0.5-9.0)	27.2 (12.9-97.2)	41.4 (12.5-136)	46.6 (13.4-179)
1 BZA 20 mg/ CE 0.625 mg Tablet (Clinical Formulation C)	Mean ± SD	3.91 ± 2.52	1.6 ± 1.7	29.3 ± 12.5	45.9 ± 25.9	51.5 ± 29.0
	%CV	64.6	106	42.8	56.5	56.3
	N	75	75	75	75	75
	Geometric Mean (Range)	3.04 (0.26-10.3)	1.2 (0.5-9.0)	27.4 (12.4-98.7)	38.6 (8.8-124)	43.6 (13.6-133)
1 BZA 20 mg/ CE 0.625 mg Tablet (Potential Commercial Formulation D)	Mean ± SD	3.88 ± 2.59	1.5 ± 1.6	28.2 ± 11.5	45.0 ± 26.0	51.1 ± 32.5
	%CV	66.6	110	40.9	57.7	63.7
	N	76	76	76	76	76
	Geometric Mean (Range)	3.02 (0.57-10.4)	1.1 (0.5-12.0)	26.4 (9.4-79.8)	38.0 (6.9-114)	42.7 (8.4-178)

Reference ID: 3319979

Table 1117-17. 90% CI for BZA

Treatment	C_{max}	t_{max}	$t_{½}$	AUC_T	AUC
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.130	.545	.290	.013	.006
Treatment	.190	.555	.527	.001	.001
Period	.137	.611	.574	.326	.201
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Clinical Formulation A (Reference) Versus Clinical Formulation B (Test)[a]					
Statistical Power (%)	91.4	79.6	-	99.7	99.7
GLS Mean Ratio	90	91	-	87	88
90% C.I.	81-100	80-104	-	81-94	81-95
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	85.4	82.2	-	94.6	96.7
GLS Mean Ratio	88	92	-	81	82
90% C.I.	78-100	81-104	-	73-90	74-90
Clinical Formulation A (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	81.5	73.9	-	96.3	97.7
GLS Mean Ratio	88	89	-	80	80
90% C.I.	77-100	77-103	-	72-88	73-88
Clinical Formulation B (Reference) Versus Clinical Formulation C (Test)[a]					
Statistical Power (%)	78.1	92.8	-	95.9	96.9
GLS Mean Ratio	98	101	-	93	93
90% C.I.	86-112	91-112	-	84-103	85-103
Clinical Formulation B (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	78.0	83.1	-	97.0	98.0
GLS Mean Ratio	98	98	-	92	92
90% C.I.	85-112	86-111	-	83-101	84-100
Clinical Formulation C (Reference) Versus Potential Commercial Formulation D (Test)[a]					
Statistical Power (%)	71.7	82.3	-	94.2	96.9
GLS Mean Ratio	99	97	-	98	98
90% C.I.	86-115	85-110	-	89-109	89-108

a. Ratio of test to reference.

Reference ID: 3319979

Table 1117-18. Overall Comparison of 90% CIs for BZA for all Formulations (Study 1117)

Formulations Compared		C_{max}	AUC
Comm Form D versus Clin Form A	Geom. Mean Ratio (%)	88	80
	90% CI	77-100	73-88
Comm Form D versus Clin Form B*	Geom. Mean Ratio (%)	**98**	**92**
	90% CI	**85-112**	**84-100**
Comm Form D versus Clin Form C*	Geom. Mean Ratio (%)	**99**	**98**
	90% CI	**86-115**	**89-108**
Clin Form B versus Clin Form A*	Geom. Mean Ratio (%)	**90**	**88**
	90% CI	**81-100**	**81-95**
Clin Form C versus Clin Form A	Geom. Mean Ratio (%)	88	82
	90% CI	78-100	74-90
Clin Form C versus Clin Form B*	Geom. Mean Ratio (%)	**98**	**93**
	90% CI	**86-112**	**85-103**

* Bold Font indicates bioequivalent formulations.

Abbreviations: C_{max} = peak concentration; AUC = total area under the concentration-time curve; Comm Form = Potential Commercial Formulation; Clin Form = Clinical Formulation; CI = confidence interval.

BZA Glucuronide (WAY-144883 and WAY-145096):

The mean PK parameters for BZA glucuronide, WAY-144883 and WAY-145096, are shown in **Table 1117-19, 1117-20**. The 90% CIs for Cmax and AUC were within the range of 80% to 125% for all comparisons (**Table 1117-19, 1117-20**).

Table 1117-19. Mean PK Parameters and 90% CI of WAY-144883 (Study 1117)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/	Mean ± SD	6.39 ± 4.84	1.6 ± 2.2	20.4 ± 9.7	48.8 ± 34.9	53.9 ± 37.4
CE 0.625 mg	%CV	75.8	138	47.6	71.6	69.4
Tablet (Clinical	N	76	76	75	76	75
Formulation A)	Geometric Mean	4.98	1.0	18.2	38.8	44.5
	(Range)	(0.76-32.9)	(0.5-16.0)	(4.9-56.6)	(2.7-187)	(10.3-213)
1 BZA 20 mg/	Mean ± SD	5.55 ± 4.20	1.4 ± 1.4	22.7 ± 11.2	45.0 ± 37.1	50.3 ± 42.8
CE 0.625 mg	%CV	75.7	103	49.5	82.5	85.2
Tablet (Clinical	N	76	76	76	76	76
Formulation B)	Geometric Mean	4.20	1.0	20.0	33.9	38.5
	(Range)	(0.42-17.7)	(0.5-9.0)	(5.6-57.1)	(3.4-212)	(4.9-238)
1 BZA 20 mg/	Mean ± SD	6.24 ± 5.46	1.3 ± 1.4	22.6 ± 13.7	43.4 ± 34.2	47.4 ± 36.1
CE 0.625 mg	%CV	87.5	112	60.8	78.9	76.1
Tablet (Clinical	N	75	75	75	75	75
Formulation C)	Geometric Mean	4.39	1.0	19.6	32.3	36.8
	(Range)	(0.41-31.7)	(0.5-9.0)	(4.5-102)	(4.7-164)	(9.3-181)
1 BZA 20 mg/	Mean ± SD	6.53 ± 6.39	1.3 ± 1.1	21.8 ± 12.0	41.4 ± 32.6	46.9 ± 39.1
CE 0.625 mg	%CV	97.8	89.7	55.2	78.8	83.3
Tablet	N	76	76	76	76	76
(Potential	Geometric Mean	4.31	1.0	19.1	31.0	35.9
Commercial	(Range)	(0.44-27.7)	(0.5-4.5)	(6.7-61.7)	(5.6-152)	(8.4-235)
Formulation D)						
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters						
Source of Variation						
Sequence		.805	.593	.364	.835	.679
Treatment		.088	.465	.174	.002	.001
Period		.126	.857	.545	.481	.638
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]						
Statistical Power (%)		82.6	73.6	-	93.1	96.5
GLS Mean Ratio		89	91	-	83	83
90% C.I.		78-101	79-104	-	75-93	75-92

Reference ID: 3319979

Table 1117-20. Mean PK Parameters and 90% CI of WAY-145096 (Study 1117)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/	Mean ± SD	122 ± 70.8	1.7 ± 2.0	17.9 ± 8.4	1247 ± 578	1319 ± 604
CE 0.625 mg	%CV	57.8	121	46.6	46.3	45.8
Tablet (Clinical	N	76	76	76	76	76
Formulation A)	Geometric Mean	104	1.3	16.1	1125	1193
	(Range)	(34.3-343)	(0.8-16.0)	(5.0-40.5)	(415-2789)	(435-2862)
1 BZA 20 mg/	Mean ± SD	113 ± 75.4	1.5 ± 1.2	18.7 ± 9.5	1143 ± 638	1208 ± 692
CE 0.625 mg	%CV	66.9	81.8	50.6	55.9	57.3
Tablet (Clinical	N	76	76	76	76	76
Formulation B)	Geometric Mean	90.6	1.2	16.6	989	1044
	(Range)	(16.0-347)	(0.8-9.0)	(5.1-45.9)	(143-3493)	(155-3824)
1 BZA 20 mg/	Mean ± SD	115 ± 75.3	1.7 ± 1.9	17.9 ± 8.0	1092 ± 609	1141 ± 626
CE 0.625 mg	%CV	65.2	110	44.6	55.8	54.9
Tablet (Clinical	N	75	75	75	75	75
Formulation C)	Geometric Mean	90.2	1.3	16.2	928	978
	(Range)	(7.8-401)	(0.5-12.0)	(6.1-38.5)	(202-2996)	(224-3015)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/	Mean ± SD	116 ± 79.4	1.4 ± 0.9	18.3 ± 9.8	1044 ± 549	1107 ± 589
CE 0.625 mg	%CV	68.7	64.3	53.4	52.5	53.3
Tablet	N	76	76	76	76	76
(Potential	Geometric Mean	90.0	1.2	16.2	906	959
Commercial	(Range)	(16.7-343)	(0.5-6.0)	(4.8-51.2)	(242-2742)	(283-2905)
Formulation D)						
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters						
Source of Variation						
Sequence		.188	.316	.119	.479	.432
Treatment		.126	.893	.702	.001	.001
Period		.247	.990	.138	.563	.694
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval						
Clinical Formulation A (Reference) Versus Clinical Formulation C (Test)[a]						
Statistical Power (%)		79.7	78.7	-	95.6	96.9
GLS Mean Ratio		87	99	-	83	82
90% C.I.		77-100	87-113	-	75-91	75-90

Conclusions:

The entire biopharmaceutics, formulation development, and associated BE studies are related to the BZA component of the product. The CE components plays small role, even if some of the components are shown to be outside the BE criteria of 80%-125%.

Therefore, in reference to the hormonal components of the product (i.e., CE layer), the tested formulations were overall equivalent, except few components.

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However, based on BZA data, Formulation B used in clinical studies 304, 305, and 306 is BE to Formulation A used in clinical studies 303 and 3307, Formulation C used in clinical study 304, and Formulation D (TBM used in four BE studies 1122, 1139, 1137, and 1142).

Also, Formulation C is BE to Formulations B and D in reference to BZA data. However, Formulation **A** is **not BE** to Formulations **D** and **C**. The bioavailability of formulation C is approximately **18%** lower than Formulation A. Formulation **D** is potential for commercial use which is BE to the clinical Formulation **B**. So based on this study the following conclusions can be made for the BZA component:

Formulation A (studies 303, 3307)	= Formulation B (studies 304, 305, 306)
Formulation B	= Formulation C (study 304)
Formulation B	= Formulation D (TBM)
Formulation C	= Formulation D (TBM)
Formulation A	≠ Formulation C (AUC is **18%** and Cmax is 12% lower than A)
Formulation A	≠ Formulation D (TBM) (AUC is 20% and Cmax is 12% lower than A

Study 1122-US (20/0.625, Formulations A, E, F, and G):

Title: "An Open-Label, Single-Dose, Randomized, 4-Period, Crossover, Bioequivalence Study of Three New Formulations of Bazedoxifene/Conjugated Estrogens Compared With a Reference Formulation in Healthy Postmenopausal Women"

Objectives: The primary objective of this study was to assess the BE of clinical and commercial formulations of BZA/CE combination tablets, assessing both the BZA and CE components. The secondary objective was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The purpose of this study was to assess the BE of 3 new formulations of BZA/CE combination tablets with a clinical formulation used in phase 3 studies (Formulation A used in studies 303 and 3307).

Design:

This was a single-dose, randomized, open-label, 4-period, 4-treatment, crossover, BE inpatient/outpatient study in 82 healthy postmenopausal female subjects (ages 47-70 years). Each single dose administration of the test and reference formulations was separated by at least a 10-day washout period. The formulations used in this study are listed below in **Table 1122-1**. It should be noted that the difference between formulation E and F is that formulation E is non-optimized and F (TBM) is optimized (b) (4) see **ONDQA review for details**).

Table 1122-1. Formulations Tested in Study 1122-US:

Test Article/Dosage Form	Strength	Formulation/ Stock Number	Batch Number
BZA/CE / Tablets Clin Form A	20 mg/0.625 mg	0931462C	2006B0313
BZA/CE / Tablets Comm Form E (FCT, (b) (4)	20 mg/0.625 mg	0932558C	C43766
BZA/CE / Tablets Comm Form F (FCT, (b) (4)	20 mg/0.625 mg	0932558C	C81416
BZA/CE / Tablets Comm Form G (FCT, (b) (4)	20 mg/0.625 mg	0932315C	C88092

BZA = bazedoxifene; CE = conjugated estrogens; Clin Form = clinical formulation; Comm Form = commercial formulation; FCT = film coated tablet; (b) (4)

All subjects were fasted overnight and until 4 hours after drug administration.

Subjects were randomly assigned to 1 of 4 sequences: A/E/F/G, E/G/A/F, F/A/G/E or G/F/E/A for the following 4 treatments:

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Treatment A (Reference): Single dose of BZA/CE (Clinical Formulation A) 20 mg/0.625 mg tablet.
Treatment E (Test): Single dose of BZA/CE (Commercial Formulation E) 20 mg/0.625 mg tablet
Treatment F (Test) BZA/CE (Commercial Formulation F) 20 mg/0.625 mg tablet
Treatment G (Test): BZA/CE (Commercial Formulation G) 20 mg/0.625 mg tablet

Blood Samples:

Blood samples for PK analysis were collected at adequate intervals over 72 hours.

Results:

Overall all estrogenic components of the product were within the BE limits. Therefore, only BZA PK data will be presented here. In addition, only formulation F was BE to Formulation A. Therefore, the focus of this review and the data to be reported in this review will be on Formulations A and F (**Tables 1122-2-3**).

Table 1122-2A. BZA PK Parameters after Administration of BZA/CE 20 mg/0.625 mg Clinical Formulation A and Commercial Formulations E, F, and G (Study 1122)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
BZA/CE 20 mg/0.625 mg Clinical Formulation A	Mean±SD	4.15±2.29	1.9±2.0	29.6±9.6	52.9±28.3	59.9±33.1
	%CV	55.1	110	32.4	53.6	55.3
	N	79	79	79	79	79
	Geometric Mean (Range)	3.50 (0.75-9.54)	1.3 (0.5-12.0)	28.2 (13.5-60.3)	46.4 (12.3-157)	52.3 (13.4-184)
BZA/CE 20 mg/0.625 mg Commercial Formulation E	Mean±SD	3.67±2.17	1.6±1.9	30.6±11.6	47.0±27.8	53.7±32.5
	%CV	59.3	117	37.9	59.2	60.6
	N	80	80	80	80	80
	Geometric Mean (Range)	2.97 (0.39-10.8)	1.2 (0.5-12.0)	28.7 (13.4-74.2)	38.9 (6.6-153)	44.3 (7.9-181)
BZA/CE 20 mg/0.625 mg Commercial Formulation F	Mean±SD	4.10±2.32	1.6±1.3	29.9±9.6	52.6±25.1	59.4±29.5
	%CV	56.6	85.0	32.0	47.7	49.6
	N	78	78	78	78	78
	Geometric Mean (Range)	3.44 (0.76-10.4)	1.3 (0.5-6.0)	28.5 (13.6-66.9)	46.7 (11.4-130)	52.4 (13.2-144)
BZA/CE 20 mg/0.625 mg Commercial Formulation G	Mean±SD	3.25±2.15	1.7±1.7	30.4±9.2	42.9±24.9	48.7±28.5
	%CV	66.4	99.2	30.2	58.0	58.5
	N	80	80	80	80	80
	Geometric Mean (Range)	2.60 (0.49-9.05)	1.3 (0.5-9.0)	29.1 (15.2-53.4)	36.0 (8.3-112)	41.1 (11.1-126)

Reference ID: 3319979

Table 1122-2B. Statistical Comparisons among BZA PK Parameters After Administration of BZA/CE 20 mg/0.625 mg Clinical Formulation A and Commercial Formulations E, F, and G (Study 1122)

Treatment	C_{max}	t_{max}	$t_{1/2}$	AUC_T	AUC
P-Values of Fixed-Effects from Mixed Effects Model of Log-Transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.929	.255	.194	.963	.904
Treatment	.001	.363	.455	.001	.001
Period	.300	.003	.057	.108	.139
Commercial Formulation E Versus Clinical Formulation A					
Statistical Power (%)	93.4	77.6	-	99.8	99.8
Geometric Least Squares Means (GLS) Ratio and Confidence Limits (CL)[a]					
GLS Means Ratio	85	88	-	84	85
90% CL	77-95	77-101	-	78-90	79-91
Commercial Formulation F Versus Clinical Formulation A					
Statistical Power (%)	79.9	75.9	-	98.2	98.7
Geometric Least Squares Means (GLS) Ratio and Confidence Limits (CL)[b]					
GLS Means Ratio	98	94	-	101	101
90% CL	86-112	82-107	-	92-111	92-110
Commercial Formulation G Versus Clinical Formulation A					
Statistical Power (%)	69.6	63.3	-	93.2	96.1
Geometric Least Squares Means (GLS) Ratio and Confidence Limits (CL)[c]					
GLS Means Ratio	75	98	-	78	79
90% CL	64-87	83-115	-	70-87	72-87

a. Ratio of Commercial Formulation E to Clinical Formulation A.
b. Ratio of Commercial Formulation F to Clinical Formulation A.
c. Ratio of Commercial Formulation G to Clinical Formulation A.

Reference ID: 3319979

Table 1122-3. Summary of the 90% Confidence Intervals for the Geometric Means Ratios (Study 1122)

Analyte	Comparison[a]	
	C_{max}	AUC
Unconjugated Estrone	96 - 106	96 - 107
Unconjugated Estrone Adjusted for Baseline	90 - 107	89 - 108
Unconjugated Equilin	91 - 104	-
Unconjugated 17β-estradiol	93 - 106	85 – 102
Unconjugated 17β-estradiol Adjusted for Baseline	86 - 103	94 - 111
Unconjugated 17β-dihydroequilin	95 - 111	102 - 120
Unconjugated $\Delta^{8,9}$-dehydroestrone	-	-
Unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol	88 - 101	-
Total Estrone	98 - 110	95 – 104
Total Estrone Adjusted for Baseline	96 - 109	91 - 103
Total Equilin	101 - 118	100 - 112
Total 17β-estradiol	99 - 117	95 – 107
Total 17β-estradiol Adjusted for Baseline	99 - 119	93 – 106
Total 17β-dihydroequilin	97 - 115	96 – 109
Total $\Delta^{8,9}$-dehydroestrone	102 - 119	103 – 115
Total 17β-$\Delta^{8,9}$-dehydroestradiol	98 - 111	97 – 110
Bazedoxifene	86 - 112	92 -110

a. Formulation F (Test) vs. Formulation A (Reference)

Conclusions:

Potential commercial formulation **F** (TBM) for 20/0.625 strength was BE to reference formulation A used in the clinical safety and efficacy studies 303 and 3307 for BZA and all measurable estrogen analytes.

Reference ID: 3319979

Study 1139-US (20/0.625, Formulations B and F "TBM"):

Title: "An Open-Label, Single-Dose, Randomized, 2-Period, Crossover, Bioequivalence Study of New Formulations of Bazedoxifene/Conjugated Estrogens Compared With a Reference Formulation in Healthy Postmenopausal Women"

Objectives: The primary objective of the study was to assess the BE of the clinical formulation used in phase 3 studies and a potential commercial formulation of BZA/CE combination tablets, assessing both the BZA and CE components.

The secondary objective of the study was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The purpose of this study was to assess the BE of a new formulation of a BZA/CE combination tablet (formulation F used in BE study 1122) with a clinical formulation B used in phase 3 studies 304, 305, and 306. Based on the BE study 1122, formulation F (TBM) was found to be bioequivalent to Formulation A used in clinical studies 303 and 3307. Therefore, this study is a similar/repeat of the BE study 1122 to compare formulation F to formulation B (i.e., not Formulation A).

Design:

This was a single-dose, randomized, open-label, 2-period, 2-treatment, crossover, inpatient/outpatient study in 90 healthy postmenopausal subjects conducted at a single investigational site. There was a minimum 10-day washout interval between each test article administration. The formulations used in this study are listed below in **Table 1139-1**.

Table 1139-1. Formulations Tested in Study 1139-US:

Drug Product	Treatment	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA/CE (FCT)	A	20/0.625	Tablets	0932558C	C81416
BZA/CE (FCT)	B	20/0.625	Tablets	0932162C	N6135

BZA = bazedoxifene; CE = conjugated estrogen; FCT = film-coated tablets.

Reference ID: 3319979

Subjects were randomly assigned to 1 of 2 sequences: A/B or B/A for the following 2 treatments:

Treatment A: Single dose of BZA/CE (Clinical Formulation **B**) 20 mg/0.625 mg tablet (reference therapy)
Treatment B: Single dose of BZA/CE (potential commercial formulation **F**) 20 mg/0.625 mg tablet (test therapy).

All subjects were fasted overnight and until 4 hours after drug administration.

Blood Samples:

Blood samples for PK analysis were collected at adequate intervals over 72 hours.

Results:

Overall most of estrogenic components of the product were within the BE limits. Therefore, only BZA PK data will be presented here (**Tables 1139-2-3**).

Table 1139-2. BZA PK Parameters Following Administration of BZA/CE 20 mg/0.625 mg Clinical Formulation B and Potential Commercial Formulation F (Study 1139)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
BZA/CE 20 mg/	Mean±SD	3.56±2.01	1.5±1.2	30.3±12.2	45.9±26.3	52.0±31.5
0.625 mg	%CV	56.4	78.9	40.2	57.4	60.5
Clinical	N	87	87	87	87	87
Formulation B	Geometric Mean	2.93	1.2	28.4	38.8	43.8
	(Range)	(0.36-11.5)	(0.5-6.0)	(14.3-95.7)	(6.1-131)	(7.5-163)
BZA/CE	Mean±SD	3.67±2.13	1.7±1.8	30.2±12.4	47.2±25.5	53.3±30.0
20 mg/0.625 mg	%CV	58.1	105	40.9	54.1	56.4
Potential	N	90	90	90	90	90
Commercial	Geometric					
Formulation F	Mean	3.14	1.3	28.2	41.0	46.6
	(Range)	(0.55-13.5)	(0.5-12.0)	(11.1-92.4)	(7.7-143)	(10.9-200)
P-Values of Fixed-Effects from Mixed Effects Model of Log-Transformed Pharmacokinetic Parameters						
Source of Variation						
Sequence		.487	.638	.780	.841	.728
Treatment		.338	.834	.459	.380	.323
Period		.501	.605	.990	.423	.448
Statistical Power (%)		86.4	92.8	-	96.2	97.6
Geometric Least Squares Means (GLS) Ratio and Confidence Limits (CL)[a]						
GLS Means Ratio		107	101	-	105	106
90% CL		95-121	91-113	-	95-116	96-116

Reference ID: 3319979

Table 1139-3. 90% CI of Geometric Mean Ratios for C_{max} and AUC for All Analytes (Study 1139)

Analyte	Comparison[a]	
	C_{max}	AUC
Unconjugated Estrone	97 - 105	94 - 102
Unconjugated Estrone Adjusted for Baseline	98 - 115	96 - 113
Unconjugated Equilin	94 - 103	-
Unconjugated 17β-estradiol	95 - 106	93 - 108
Unconjugated 17β-estradiol Adjusted for Baseline	98 - 118	90 - 112
Unconjugated 17β-dihydroequilin	96 - 107	97 - 110
Unconjugated $\Delta^{8,9}$-dehydroestrone	-	-
Unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol	88 - 101	-
Total Estrone	95 - 105	94 - 102
Total Estrone Adjusted for Baseline	94 - 105	91 - 104
Total Equilin	96 - 110	98 - 109
Total 17β-estradiol	99 - 112	96 - 107
Total 17β-estradiol Adjusted for Baseline	99 - 113	95 - 109
Total 17β-dihydroequilin	96 - 108	100 - 111
Total $\Delta^{8,9}$-dehydroestrone	97 - 109	98 - 109
Total 17β-$\Delta^{8,9}$-dehydroestradiol	98 - 109	99 - 111
Bazedoxifene	95 - 121	96 - 116

a. Formulation F (Test) vs. Formulation B (Reference)

Conclusions:

As stated in the various Sections of this review, Formulation B was used in the phase 3 safety and efficacy studies 304, 305, and 306. The previous study 1122 had shown that the formulation F used in this study was BE to formulation A used in studies 303 and 3307. This study confirms that formulation F (TBM) is also BE to formulation B for 20/0.625 strength.

Study 1137-US (20/0.45, Formulations A, 1, 2, and 3):

Title: "An Open-Label, Single-Dose, Randomized, 4-Period, Crossover, Bioequivalence Study of Three New Formulations of Bazedoxifene/Conjugated Estrogens Compared With a Reference Formulation in Healthy Postmenopausal Women"

Objectives: The primary objective of the study was to assess the BE of test and reference formulations of BZA/CE combination tablets, assessing both the BZA and CE components. The secondary objective was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The purpose of this study was to assess the bioequivalence of 3 new test therapies of BZA/CE combination tablets with a reference therapy used in phase 3 studies.

Design:

This was a single-dose, randomized, open-label, 4-period, 4-treatment, crossover, inpatient/outpatient study in 90 healthy postmenopausal subjects. There was at least a 10-day washout between single dose administrations of the test articles.

The formulations used in this study are listed below in **Table 1137-1**.

Table 1137-1. Formulations Tested in Study 1137-US:

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA/CE (reference therapy)	20/0.45mg	Tablet	0931525C	2008B0190
BZA/CE 24 mg (b) (4) (test therapy 1)	20/0.45mg	Tablet	0932557C	D87931
BZA/CE 23 mg (b) (4) (test therapy 2)	20/0.45mg	Tablet	0932780C	D87932
BZA/CE 25 mg (b) (4) (test therapy 3)	20/0.45mg	Tablet	0932797C	D87933

Abbreviation: (b) (4)

All subjects were fasted overnight and until 4 hours after drug administration.

Subjects were randomly assigned to 1 of 4 treatment sequences: 1/2/3/4, 2/4/1/3, 3/1/4/2, or 4/3/2/1 where:

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Treatment 1: BZA/CE 20 mg/0.45 mg tablet (reference therapy);
Treatment 2: BZA/CE 20 mg/0.45 mg, **24** mg [redacted] tablet (test therapy 1);
Treatment 3: BZA/CE 20 mg/0.45 mg, **23** mg [redacted] tablet (test therapy 2);
Treatment 4: BZA/CE 20 mg/0.45 mg, **25** mg [redacted] tablet (test therapy 3).

Blood Samples:

Blood samples for PK analysis were collected at adequate intervals over 72 hours.

Results:

Overall most estrogenic components of the product were within the BE limits. Therefore, only BZA PK data will be presented here (**Tables 1137-2-4**).

Table 1137-2. BZA Pharmacokinetic Parameters Following Single Dose Administration of a BZA 20 mg/CE 0.45 mg Tablet as Reference Therapy A and Three Test Therapies

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Reference Therapy A	Mean±SD	3.81±1.80	1.8±1.6	27.4±8.0	51.3±24.0	56.9±26.7
	%CV	47.3	87.8	29.2	46.9	46.8
	N	89	89	89	89	89
	Geometric Mean	3.37	1.3	26.3	46.2	51.3
	(Range)	(0.70-8.55)	(0.5-6.0)	(13.9-53.7)	(15.2-127)	(17.1-143)
Test Therapy 1 [redacted]	Mean±SD	4.13±2.16	1.6±1.5	28.3±8.9	54.6±29.3	61.1±32.9
	%CV	52.3	90.6	31.3	53.7	53.8
	N	88	88	88	88	88
	Geometric Mean	3.55	1.3	27.0	47.8	53.5
	(Range)	(0.93-9.32)	(0.8-6.0)	(13.0-56.0)	(15.6-166)	(18.2-175)
Test Therapy 2 [redacted]	Mean±SD	3.86±2.06	1.9±2.2	27.2±8.2	50.8±28.8	56.5±32.7
	%CV	53.5	117.2	30.0	56.7	57.8
	N	90	90	90	90	90
	Geometric Mean	3.29	1.3	26.0	43.6	48.5
	(Range)	(0.57-10.3)	(0.5-12.0)	(14.2-51.6)	(9.4-168)	(11.1-196)
Test Therapy 3 [redacted]	Mean±SD	3.79±2.12	1.9±1.8	28.0±11.0	50.5±25.7	56.6±29.5
	%CV	56.0	95.4	39.2	50.9	52.2
	N	89	89	89	89	89
	Geometric Mean	3.23	1.4	26.5	43.7	48.8
	(Range)	(0.94-10.3)	(0.5-9.0)	(13.7-94.1)	(8.9-139)	(10.6-148)
P-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters						
Source of Variation						
Sequence		0.189	0.521	0.283	0.442	0.458
Treatment		0.347	0.542	0.111	0.047	0.021
Period		0.417	0.104	0.962	0.767	0.773

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Table 1137-3 (continued). BZA Pharmacokinetic Parameters Following Single Dose Administration of a BZA 20 mg/CE 0.45 mg Tablet as Reference Therapy A and Three Test Therapies

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval. Test Therapy 1 ([(b) (4)]) Vs. Reference Therapy A[a]					
Statistical Power (%)	96.7	72.5	-	99.9	100.0
GLS Mean Ratio	106	95	-	104	105
90% C.I.	96-117	82-109	-	97-112	98-112
Test Therapy 2 ([(b) (4)]) Vs. Reference Therapy A[a]					
Statistical Power (%)	94.1	69.5	-	99.9	100.0
GLS Mean Ratio	98	97	-	94	94
90% C.I.	88-108	84-113	-	88-101	88-101
Test Therapy 3 ([(b) (4)]) Vs. Reference Therapy A[a]					
Statistical Power (%)	91.8	85.8	-	99.8	99.9
GLS Mean Ratio	96	106	-	95	95
90% C.I.	86-108	94-120	-	88-102	88-102
Test Therapy 2 ([(b) (4)]) Vs. Test Therapy 1 ([(b) (4)])					
Statistical Power (%)	97.4	79.4	-	100.0	100.0
GLS Mean Ratio	92	103	-	90	90
90% C.I.	84-101	90-117	-	84-97	84-96
Test Therapy 3 ([(b) (4)]) Vs. Test Therapy 1 ([(b) (4)])					
Statistical Power (%)	94.4	76.9	-	99.8	99.9
GLS Mean Ratio	91	112	-	91	91
90% C.I.	82-101	98-128	-	84-98	84-97
Test Therapy 3 ([(b) (4)]) Vs. Test Therapy 2 ([(b) (4)])					
Statistical Power (%)	90.9	79.5	-	99.5	99.7
GLS Mean Ratio	99	109	-	101	101
90% C.I.	88-110	96-125	-	93-109	93-109

Note:
Treatment 1: BZA/CE 20 mg/0.45 mg tablet (reference therapy);
Treatment 2: BZA/CE 20 mg/0.45 mg tablet, [(b) (4)] test therapy 1);
Treatment 3: BZA/CE 20 mg/0.45 mg tablet, test therapy 2);
Treatment 4: BZA/CE 20 mg/0.45 mg tablet, test therapy 3).

a. Ratio of test to reference.
b. Ratio of Test Therapy 2 to Test Therapy 1.
c. Ratio of Test Therapy 3 to Test Therapy 1.
d. Ratio of Test Therapy 3 to Test Therapy 2.

Table 1137-4. 90% CI of Geometric Mean Ratios for C_{max} and AUC for All Analytes (Study 1137)

Analyte	Comparison A		Comparison B		Comparison C	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Unconjugated Estrone	104-113	96-106	102-111	94-101	105-115	96-106
Unconjugated Estrone Adjusted for Baseline	111-128	102-123	107-122	92-109	109-128	95-114
Unconjugated Equilin	101-114	-	99-112	-	102-118	-
Unconjugated 17β-estradiol	103-111	92-107	99-108	86-102	101-110	88-102
Unconjugated 17β-estradiol Adjusted for Baseline	111-129	93-119	100-122	89-116	105-127	95-120
Unconjugated 17β-dihydroequilin	109-122	87-103	104-118	88-102	104-118	93-110
Unconjugated $\Delta^{8,9}$-dehydroestrone	-	-	-	-	-	-
Unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol	95-114	-	94-112	-	97-115	-
Total Estrone	106-120	98-107	100-114	95-104	104-119	96-103
Total Estrone Adjusted for Baseline	108-123	99-110	100-116	92-104	105-122	94-105
Total Equilin	107-124	101-110	91-105	89-101	90-102	87-98
Total 17β-estradiol	91-105	89-101	90-102	87-98	96-109	92-102
Total 17β-estradiol Adjusted for Baseline	91-107	90-104	90-104	88-103	96-111	92-104
Total 17β-dihydroequilin	107-123	98-110	101-116	95-106	104-119	97-106
Total $\Delta^{8,9}$-dehydroestrone	111-127	99-111	104-119	95-106	106-121	98-110
Total 17β-$\Delta^{8,9}$-dehydroestradiol	103-117	99-111	100-112	97-106	102-115	99-110
Bazedoxifene	96-117	98-112	88-108	88-101	86-108	88-102

A: Test Therapy 1 (b) (4) vs. Therapy A (Reference).
B: Test Therapy 2 vs. Therapy A (Reference).
C: Test Therapy 3 vs. Therapy A (Reference).

Conclusions:

All 3 test therapies were BE to reference therapy A for BZA (C_{max} and AUC). Formulation 2 for 20/0.45 mg strength (b) (4) was bioequivalent to reference formulation A 20/0.45 mg strength used in studies 303 and 3307 at all measurable estrogen analytes.

Test Therapies 1 (b) (4) and 3 (b) (4) were BE to reference formulation A for all measurable estrogen analytes **except** unconjugated estrone adjusted for baseline and unconjugated 17 β -estradiol adjusted for baseline. For these comparisons the upper limits of the CIs for C_{max} were greater than 125. Additionally, the upper limit of the CI for C_{max} comparing test Therapy 1 to the reference was higher than 125 for total dehydroestrone.

Based on these data, Formulation 2 for 20/0.45 mg strength (b) (4) which is BE to formulation A was selected as the proposed TBM formulation.

Study 1142-US (20/0.45, Formulations B, 1, 2, and 3):

Title: "An Open-Label, Single-Dose, Randomized, 4-Period, Crossover, Bioequivalence Study of Four New Formulations of Bazedoxifene/Conjugated Estrogens Compared With a Reference Formulation in Healthy Postmenopausal Women"

Objectives: The primary objective was to assess the BE of test and reference formulations of BZA/CE combination tablets, assessing both the BZA and CE components.
The secondary objective was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The purpose of this study was to assess the BE of test formulations of BZA/CE combination tablets with a reference formulation used in phase 3 studies.

Basically this study is a repeat of study 1137 except the reference formulation is formulation B at 20/0.45 mg strength used in the safety and efficacy studies 304, 305, and 306. The test formulations (**Table 1142-1**) are the same as those used in study 1137 (formulation 1, 2, and 3 at 20/0.45 mg strength).

Design:

This was a single-dose, randomized, open-label, 4-period, 4-treatment, crossover, inpatient/outpatient study in 88 healthy postmenopausal subjects. There was at least a 10-day washout between single dose administrations of each formulation. Each subject participated in the study for approximately 8 weeks.

The formulations used in this study are listed below in **Table 1142-1A and B**.

Table 1142-1A. Formulations Tested in Study 1142-US:

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
Treatment 1 BZA/CE (Test Formulation 1 (b) (4))	BZA: 20 mg CE: 0.45 mg	Tablet	0932780C	D87932
Treatment 2 BZA/CE (Test Formulation 2 (b) (4))	BZA: 20 mg CE: 0.45 mg	Tablet	0932557C	D87931
Treatment 3 BZA/CE (Test Formulation 3 (b) (4))	BZA: 20 mg CE: 0.45 mg	Tablet	0932797C	D87933
Treatment 4 BZA/CE (Reference Formulation B)	BZA: 20 mg CE: 0.45 mg	Tablet	0932161C	N6137 (b) (4)

Abbreviations: BZA = bazedoxifene; CE = conjugated estrogens

Reference ID: 3319979

It should be noted that formulations 1 and 2 in studies 1137 and 1142 are the same. However, it is very confusing as formulation 1 in this study 1142 (b) (4) ***with the batch number D87932 has the same batch number (D87932) for formulation 2*** (b) (4) ***in study 1137 (Table 1142-1B). Therefore, it is not clear which formulation*** (b) (4) ***and which is the corresponding batch number.***

Table 1142-1 B. Formulations Used in Studies 1137 and 1142

Formulations	Study 1137		Study 1142	
	(b) (4)	Batch #	(b) (4)	Batch #
Reference		Formulation A 2008B0190		Formulation B N6137
Formulation 1		D87931		D87932
Formulation 2		D87932		D87931
Formulation 3		D87933		D87933

All subjects were fasted overnight and until 4 hours after drug administration.

Subjects were randomly assigned to 1 of the following 4 treatments:

Treatment 1: BZA/CE 20 mg/0.45 mg tablet (test formulation 1 (b) (4))
Treatment 2: BZA/CE 20 mg/0.45 mg tablet (test formulation 2 (b) (4))
Treatment 3: BZA/CE 20 mg/0.45 mg tablet (test formulation 3 (b) (4))
Treatment 4: BZA/CE 20 mg/0.45 mg tablet (reference formulation B)

Blood Samples:

Blood samples for PK analysis were collected at adequate intervals over 72 hours.

Results:

Overall all estrogenic components of the product were within the BE limits. Therefore, only BZA PK data will be presented here (**Tables 1142-2-3**).

Table 1142-2. PK Parameters for BZA Following Single Dose Administration of a BZA 20-mg/CE-0.45 mg Tablet as 3 Test Formulations and Reference Formulation B (Study 1142)

Treatment		C_{max} (ng/mL)	t_{max} (h)	$T_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
Test Formulation 1 (b) (4)	Mean±SD	3.25±2.01	1.7±1.9	29.0±9.1	45.7±24.9	51.6±28.5
	%CV	61.8	112	31.4	54.6	55.3
	N	84	84	84	84	84
	Geometric Mean (Range)	2.68 (.63-9.21)	1.3 (0.5-12.0)	27.6 (14.4-58.6)	39.8 (10.7-117)	45.2 (16.5-149)
Test Formulation 2 (b) (4)	Mean±SD	3.75±1.88	1.4±1.2	29.4±10.5	49.7±25.5	56.3±30.0
	%CV	50.1	83.3	35.9	51.2	53.4
	N	85	85	85	85	85
	Geometric Mean (Range)	3.19 (.43-8.29)	1.1 (0.5-6.0)	27.9 (16.0-77.2)	43.4 (10.2-125)	49.3 (16.8-156)
Test Formulation 3 (b) (4)	Mean±SD	3.61±1.79	1.7±1.7	29.9±11.5	54.4±43.4	63.4±61.9
	%CV	49.6	99.2	38.6	79.9	97.7
	N	87	87	87	87	87
	Geometric Mean (Range)	3.15 (.82-8.12)	1.3 (0.5-9.0)	28.2 (16.6-77.8)	46.3 (14.5-390)	52.5 (17.0-563)
Reference Formulation B	Mean±SD	3.51±2.83	1.9±1.8	29.4±11.6	47.9±28.9	53.8±32.3
	%CV	80.8	98.5	39.4	60.3	60.0
	N	86	86	86	86	86
	Geometric Mean (Range)	2.67 (.47-17.6)	1.4 (0.8-12.0)	27.7 (15.6-73.1)	39.8 (9.0-140)	45.0 (12.1-161)

Treatment	C_{max} (ng/mL)	t_{max} (h)	$T_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
p-Values of Fixed Effects from Mixed Effects Model of Log-transformed Pharmacokinetic Parameters					
Source of Variation					
Sequence	.910	.316	.312	.540	.469
Treatment	.004	.200	.959	.009	.009
Period	.072	.847	.474	.734	.913
Statistical Power, Geometric Least Squares (GLS) Means Ratios and Ordinary Confidence Interval					
Test Formulation 1 Vs. Reference Formulation B[a]					
Statistical Power (%)	81.7	68.1	-	95.6	96.7
GLS Mean Ratio	99	91	-	99	99
90% C.I.	87-113	78-106	-	89-109	90-109
Test Formulation 2 Vs. Reference Formulation B[a]					
Statistical Power (%)	81.3	69.3	-	97.1	97.8
GLS Mean Ratio	119	83	-	109	110
90% C.I.	105-135	71-96	-	99-120	100-120
Test Formulation 3 Vs. Reference Formulation B[a]					
Statistical Power (%)	87.3	85.0	-	97.9	98.7
GLS Mean Ratio	116	93	-	114	113
90% C.I.	103-131	82-105	-	104-124	104-124

a. Ratio of test formulation to Reference Formulation B.

Reference ID: 3319979

Table 1142-3. Summary of the 90% Confidence Intervals for the Geometric Means Ratios (Study 1142)

	Comparison A		Comparison B		Comparison C	
Analyte	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Unconjugated Estrone	94 - 102	93 – 105	94 – 102	93 – 105	94 - 102	93 – 105
Unconjugated Estrone Adjusted for Baseline	92 – 105	91 – 112	82 – 98	84 – 103	88 - 105	85 – 104
Unconjugated Equilin	92 – 103	-	91 – 103	-	94 – 106	-
Unconjugated 17β-estradiol	90 – 103	97 – 99	92 – 102	91 – 108	92 - 105	91 – 112
Unconjugated 17β-estradiol Adjusted for Baseline	89 – 107	91 – 119	89 – 110	90 – 118	91 - 110	88 – 117
Unconjugated 17β-dihydroequilin	96 – 108	92 – 107	93 – 107	90 – 105	97 - 110	87 – 104
Unconjugated $\Delta^{8,9}$-dehydroestrone	-	-	-	-	-	-
Unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol	-	-	-	-	-	-
Total Estrone	90 – 98 –	95 – 102	90 – 99	94 – 101	91 - 101	92 – 101
Total Estrone Adjusted for Baseline	86 – 100	95 – 108	92 – 102	93 – 109	92 - 104	93 – 108
Total Equilin	93 – 103	97 – 106	92 – 103	94 – 104	92 - 104	92 – 103
Total 17β-estradiol	91 – 103	93 – 103	88 – 101	89 – 100	87 - 100	87 – 98
Total 17β-estradiol Adjusted for Baseline	88 – 105	89 – 103	90 – 104	90- 105	89 - 102	85 – 100
Total 17β-dihydroequilin	95 – 104	97 – 108	93 – 104	95 – 105	94 - 107	94 – 107
Total $\Delta^{8,9}$-dehydroestrone	94 – 103	100-107	91 – 100	94 – 104	93 - 103	94 – 103
Total 17β-$\Delta^{8,9}$-dehydroestradiol	92 - 99	97 – 107	95 – 107	95 – 106	97 - 108	96 – 110
Bazedoxifene	87-113	90-109	105-135	100-120	103-131	104-124

Comparison A: [redacted] (b) (4) vs. Formulation B (Reference)
Comparison B: [redacted] vs. Formulation B (Reference)
Comparison C: [redacted] vs. Formulation B (Reference)

Conclusions:

Only test Formulation 1 [redacted] (b) (4) was BE to Reference Formulation B used in studies 303, 305, and 306 for estrogen and BZA. It is believed that this is same formulation [redacted] (b) (4) that was also bioequivalent to reference formulation A used in studies 303 and 3307.

Study 1143-US (20/0.45, [redacted] PCF "reference", and Formulations 1, 2, and 3):

Title: "An Open-Label, Single-Dose, Randomized, 4-Period, Crossover, Bioavailability Study of three Test Formulations of Bazedoxifene/Conjugated Estrogens [redacted] Compared with a Reference Formulation in Healthy Postmenopausal Women"

Objectives: The primary objective of this study was to assess the BA of the BZA component of 3 test formulations of BZA/CE [redacted] compared with a potential market (reference) formulation of BZA/CE combination tablets. The secondary objective was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The purpose of this study was to assess the relative BA of the BZA component of 3 formulations of BZA/CE [redacted] compared with a reference formulation [redacted] (a potential market formulation). [redacted]

Design:

This was a single-dose, randomized, open-label, 4-period, 4-treatment, crossover, BE inpatient/outpatient study in 37 healthy postmenopausal female subjects. This study was conducted at a single investigational site, and healthy postmenopausal women aged 35 to 70 years inclusive.

Each subject received a single oral dose of a different test article during each of 4 treatment periods. Each treatment was administered after an overnight fast of at least 10 hours and at approximately 0800 hours on study day 1. Each dose of test article was administered as a single tablet with 240 mL of water. Subjects continued to fast until 4 hours after test formulation administration. Each dose was separated by a washout interval of at least 10 days. Subjects were randomized to the following treatments:

Treatment 1: Single dose of BZA/CE 20 mg/0.45 mg tablet (test formulation 1 [redacted]).
Treatment 2: Single dose of BZA/CE 20 mg/0.45 mg tablet (test formulation 2 [redacted]).
Treatment 3: Single dose of BZA/CE 20 mg/0.45 mg tablet (test formulation 3 [redacted]).
Treatment 4: Single dose of BZA/CE 20 mg/0.45 mg tablet (reference therapy, potential market formulation [redacted]).

The formulations used in this study are listed below in **Table 1143-1**.

Reference ID: 3319979

Table 1143 A. Formulation Tested in Study 1143-US

Test Article Dosage Form	Strength	Formulation/ Stock Number	Batch Number
Treatment 1, Test Formulation 1, BZA/CE[a] Tablets	20 mg/0.45 mg	0932776C	2008B0240
Treatment 2, Test Formulation 2 BZA/CE[b] Tablets	20 mg/0.45 mg	0932778C	2008B0242
Treatment 3, Test Formulation 3 BZA/CE[c] Tablets	20 mg/0.45 mg	0932777C	2008B0241
Treatment 4, Reference Therapy BZA/CE[d] Tablets	20 mg/0.45 mg	0932774C	2008B0235

a. (b) (4)
b.
c.
d.

Blood Samples:

Blood samples for BZA PK analysis were collected at adequate intervals over 96 hours. In this study, the plasma concentrations of CE components were not performed.

Results:

As stated above, only plasma concentration of BZA was determined in this study. **Tables 1143-2 and 3** show the summaries of BZA PK and statistical data.

Table 1143-2. PK Parameter Estimates of BZA Following Administration of a Single 20 mg/0.45 mg Dose of BZA/CE with Varying Amounts of (b) (4)

Mean ± SD	(b) (4) (n=36)	(b) (4) (n=36)	(b) (4) (n=36)	Reference (b) (4) (n=36)
C_{max} (ng/mL)	6.78 ± 2.41	6.24 ± 2.76	6.81 ± 2.07	6.55 ± 2.75
t_{max}[a] (h)	0.75 (0.75 - 2.00)	0.75 (0.50 - 12.00)	0.76 (0.75 - 1.58)	0.78 (0.50 - 3.00)
$t_{1/2}$ (h)	32.22 ± 13.61	28.61 ± 8.57	31.13 ± 10.99	30.34 ± 9.39
AUC_T (ng•h/mL)	82.2 ± 34.6	76.5 ± 33.3	77.1 ± 32.2	77.1 ± 33.9
AUC (ng•h/mL)	94.8 ± 41.7	85.8 ± 40.5	88.1 ± 39.7	85.9 ± 37.1

Table 1143-3. PK Statistical Comparison of BZA Following Administration of a Single 20 mg/0.45 mg Dose of BZA/CE in a Crossover Design with Varying Amounts of (b) (4) (b) (4)

p-Values from Log-Transformed Analysis of Variance			
Factor	C_{max} (ng/mL)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
Period	0.316	0.291	0.129
Sequence	0.167	0.471	0.582
Treatment	0.266	0.257	0.0675
Intersubject %CV	24.9	40.4	42.7
Intrasubject %CV	33.6	19.1	19.2
Pairwise Comparison: (b) (4) **(Test) versus Reference (Ref.)**			
Ratio of Least Square Geometric Means (%)	93	98	98
90% Confidence Interval around Ratio	82-106	91-106	91-105
Probability < 80%	0.0228	0.00000481	0.0000103
Probability > 125%	0.000137	0.000000250	0.000000160
Total Probability (<80%, >125%)	0.0229	0.00000506	0.0000104
Statistical Power (%)	89.0	99.9	99.9
Pairwise Comparison: (b) (4) **(Test) versus Reference (Ref.)**			
Ratio of Least Square Geometric Means (%)	106	107	110
90% Confidence Interval around Ratio	93-120	99-115	102-118
Probability < 80%	0.000227	0.00	0.00
Probability > 125%	0.0162	0.000360	0.00211
Total Probability (<80%, >125%)	0.0165	0.000360	0.00211
Statistical Power (%)	89.0	99.9	99.9
Pairwise Comparison: (b) (4) **(Test) versus Reference (Ref)**			
Ratio of Least Square Geometric Means (%)	107	101	101
90% Confidence Interval around Ratio	95-122	93-108	94-109
Probability < 80%	0.000111	0.000000690	0.000000380
Probability > 125%	0.0262	0.00000185	0.00000450
Total Probability (<80%, >125%)	0.0263	0.00000254	0.00000488
Statistical Power (%)	89.0	99.9	99.9

Conclusions:

Based on this study, the 90% CI for BZA data for all treatments were within the range of 80% to 125% for both Cmax and AUC. Therefore, the test formulations are considered to be BE to the reference formulation in terms of BZA Cmax and AUC. Thus, the specified allowable levels (b) (4) are sufficient to ensure BE to the potential market formulation.

Reference ID: 3319979

Study 114-US (20/0.0.625, Formulation A and Formulation C):

Title: "An Open-Label, Single-Dose, Randomized-to-sequence, 2-Period, Crossover, Pivotal Bioequivalence Study Between Bazedoxifene Acetate/Conjugated Estrogens (Premarin current process) and Bazedoxifene Acetate/Conjugated Estrogens (Premarin new process) Tablets Administered to Healthy Postmenopausal Women"

Objectives: The primary objective of the study was to assess the potential BE between BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.
The secondary objective of the study was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The term Premarin Current Process (PCP) refers to the [redacted] (b) (4) BZA/CE combination tablets used in the earlier phase 1, 2, and 3 studies. The purpose of this study was to determine the BE of BZA/CE combination tablets having the PCP [redacted] (b) (4) with BZA/CE combination tablets having a reformulated Premarin New Process (PNP) [redacted] (b) (4)

Design:

This was an open-label, single-dose, randomized-to-sequence, 2-period crossover, inpatient/outpatient study performed at a single investigational site in 72 postmenopausal women. Each subject participated in the study for approximately 38 days. Each of 2 treatment periods included a 4-day/3-night inpatient confinement period.

Each subject received a single oral dose of a different test article during each of 2 treatment periods. Each treatment was administered after an overnight fast of at least 10 hours and at approximately 0800 hours on study day 1. Each dose of test article was administered as a single tablet with 240 mL of water. Subjects continued to fast until 4 hours after test formulation administration. Each dose was separated by a washout interval of at least 10 days. Subjects were randomized to the following treatments:

Treatment A: Single dose of BZA/CE 20 mg/0.0.625 mg tablet (PCP) tablet (**Formulation A**).

Treatment B: Single dose of BZA/CE 20 mg/0.625 mg tablet (PNP) tablet (**Formulation C**)

The formulations used in this study are listed below in **Table 114-1**.

Table 114-1. Formulations Tested in Study 114-US:

Study Drug	Dosage (mg)	Formulation Number	Batch Number
BZA/CE (PCP) tablet	20 mg/0.625 mg	0931462C	2006B0313
BZA/CE (PNP) tablet	20 mg/0.625 mg	0932315C	P6208

BZA = bazedoxifene; CE = conjugated estrogens; PCP = Premarin Current Process; PNP = Premarin New

Reference ID: 3319979

Blood Samples:

Blood samples for BZA/CE PK analysis were collected at adequate intervals over 96 hours.

Results:

The focus of this study is on the PK of BZA. **Tables 114-2 and 3** show the summaries of BZA PK and statistical data.

Table 114-2. PK Parameter Estimates of BZA Following Administration of a Single 20 mg/0.625 mg Dose of BZA/CE

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
1 BZA 20 mg/CE 0.625 mg tablet (PCP)	Mean ± SD	3.39 ± 1.99	1.8 ± 1.8	31.6 ± 16.6	50.6 ± 26.1	57.5 ± 29.0
	%CV	58.8	99.9	52.3	51.6	50.5
	N	71	71	71	71	71
	Geometric mean	2.90	1.3	29.1	44.7	50.9
	(Range)	(0.68-12.1)	(0.5-9.0)	(16.6-128)	(9.9-137)	(11.7-147)
1 BZA 20 mg/CE 0.625 mg tablet (PNP)	Mean ± SD	3.27 ± 2.20	1.6 ± 1.4	29.5 ± 11.2	45.7 ± 30.1	51.6 ± 33.6
	%CV	67.3	85.5	38.1	65.9	65.2
	N	71	71	71	71	70
	Geometric mean	2.44	1.3	27.8	34.4	40.0
	(Range)	(0.25-9.38)	(0.5-6.0)	(9.7-82.5)	(1.1-124)	(1.8-149)
p-Values of Fixed Effects From Mixed-Effects Model of Log-Transformed Pharmacokinetic Parameters						
Source of variation						
Sequence		0.406	0.255	0.071	0.206	0.103
Treatment		0.057	0.611	0.167	0.002	0.001
Period		0.187	0.109	0.660	0.182	0.094
Statistical Power (%)		69.5	62.6	-	77.0	85.6
Geometric Least Squares (GLS) Mean Ratio and Confidence Limits (CLs)[a]						
GLS mean ratio		84	95	-	77	78
90% CLs		73-98	81-112	-	67-88	69-88

Reference ID: 3319979

Table 114-3. Geometric Least Squares Mean Ratios and 90% Confidence Limits of BZA and CE Following Administration of a Single 20 mg/0.625 mg Dose of BZA/ CE

Analyte	C_{max}	AUC_T	AUC
Unconjugated estrone	105 (99-111)	99 (94-104)	103 (97-109)
Unconjugated estrone adjusted for baseline	105 (97-113)	88 (78-98)	89 (79-102)
Unconjugated equilin	100 (94-106)	99 (88-115)	-
Total estrone	103 (96-110)	99 (93-105)	96 (90-102)
Total estrone adjusted for baseline	102 (95-110)	96 (90-102)	92 (86-100)
Total equilin	98 (95-110)	100 (94-107)	97 (90-104)
Bazedoxifene	84 (73-98)	77 (67-88)	78 (69-88)

Conclusions:

Based on this study, the 90% CI for BZA data were outside the range of 80% to 125% for both Cmax and AUC. The Cmax of BZA for PNP formulation (test, Formulation C) was approximately 16% lower than the reference formulation (PCP, Formulation A). Similarly, the AUC for Formulation C (PNP) was approximately 22% lower than Formulation A (PCP). Therefore, it can be concluded that the two formulations are not BE.

Study 1120-US (20/0.0.625, Formulation A and Formulation C, Partial replicate Design):

Title: "An Open-Label, Single-Dose, Randomized, 3-Period, Crossover, Bioequivalence Study Between Bazedoxifene Acetate/Conjugated Estrogens (Premarin current process) and Bazedoxifene Acetate/Conjugated Estrogens (Premarin new process) Tablets Administered to Healthy Postmenopausal Women"

Objectives: The primary objective of the study was to assess the potential BE between BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.
The secondary objective of the study was to obtain additional safety and tolerability data concerning BZA/CE in healthy postmenopausal women.

Rationale:

The term Premarin Current Process (PCP) refers to the [redacted] (b) (4) BZA/CE combination tablets used in the earlier phase 1, 2, and 3 studies. The purpose of this study was to determine the BE of BZA/CE combination tablets having the PCP [redacted] (b) (4) with BZA/CE combination tablets having a reformulated Premarin New Process (PNP) [redacted] (b) (4).

Design:

This was an open-label, single-dose, randomized, 3-period, 2 treatment, replicate design, crossover, inpatient/outpatient study in 72 postmenopausal women. Only BZA samples were collected in period 3 for PK analysis.

The randomized crossover design was selected by the sponsor because PK effects can be compared within subjects using the intrasubject variability instead of between subjects using the total (intrasubject plus intersubject) variability, thereby reducing the number of subjects required to attain the desired statistical power. In addition, for BZA, a 3-period design in comparison to a 2-period design was to have higher power to demonstrate BE for the same sample size and to allow estimation of all population variances.

Each subject received a single oral dose of a different test article during each treatment period. Each treatment was administered after an overnight fast of at least 10 hours and at approximately 0800 hours on study day 1. Each dose of test article was administered as a single tablet with 240 mL of water. Subjects continued to fast until 4 hours after test formulation administration. Each dose was separated by a washout interval of at least 10 days. Subjects were randomly assigned to 1 of 2 sequences, A/B/A or B/A/B for the following 2 treatments:

Treatment A: Single dose of BZA/CE 20 mg/0.0.625 mg tablet (PNP) tablet
(Test **Formulation C**).

Treatment B: Single dose of BZA/CE 20 mg/0.625 mg tablet (PCP) tablet
(Reference **Formulation A**)

Reference ID: 3319979

The formulations used in this study are listed below in **Table 1120-1**.

Table 1120-1. Formulations Tested in Study 1120-US:

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA/CE (PCP)	20.0/0.625	Tablet	0931462C	W92631A
BZA/CE (PNP)	20.0/0.625	Tablet	0932315C	2002B0199

Blood Samples:

Blood samples for BZA/CE PK analysis were collected at adequate intervals over 96 hours.

Results:

The focus of this study is on the PK of BZA. **Tables 1120-2 and 4** show the summaries of BZA PK and statistical data.

Table 1120-2. PK Parameter Estimates of BZA Following Administration of a Single 20 mg/0.625 mg Dose of BZA/CE

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_T (ng•h/mL)	AUC (ng•h/mL)
BZA/CE 20 mg/0.625 mg (PNP)	Mean±SD	3.72±2.60	1.7±1.6	32.5±17.4	41.1±29.2	47.0±31.0
	%CV	69.9	90.9	53.5	71.0	65.9
	N	105	105	104	105	104
	Geometric Mean	2.79	1.3	29.7	31.3	37.7
	(Range)	(0.21-13.7)	(0.5-6.0)	(8.8-139)	(3.1-165)	(4.7-171)
BZA/CE 20 mg/0.625 mg (PCP)	Mean±SD	4.04±1.96	1.7±1.3	30.1±10.9	50.2±23.4	56.8±26.7
	%CV	48.4	77.5	36.2	46.6	47.1
	N	104	104	104	104	104
	Geometric Mean	3.61	1.4	28.4	45.5	51.3
	(Range)	(0.64-12.7)	(0.5-6.0)	(11.4-72.6)	(11.2-135)	(14.8-142)
p-Values of Fixed Effects from Mixed-Effects Model of Log-Transformed Pharmacokinetic Parameters						
Source of Variation						
Trt_A		0.001	0.001	0.001	0.001	0.001
Trt_B		0.001	0.001	0.001	0.001	0.001
Tau_1		0.146	0.038	0.876	0.394	0.337
Tau_2		0.255	0.140	0.789	0.597	0.538
Tau_3		0.203	0.109	0.153	0.287	0.433
Carry		0.420	0.176	0.196	0.396	0.279
Statistical Power (%)		71.0	67.7	-	81.8	91.0
Geometric Least Squares (GLS) Means Ratio and Confidence Interval (CI)[a]						
GLS Means Ratio		78	95	-	70	74
90% CI		68-91	82-111	-	62-80	66-83

Reference ID: 3319979

Table 1120-3. Variance Components

		PNP	PCP
C_{max}			
	Between	0.4120	0.0684
	Within	0.2463	0.1846
AUC			
	Between	0.3443	0.1303
	Within	0.1651	0.0934

Table 1120-4. Geometric Least Squares Mean Ratios and 90% Confidence Limits of BZA and CE Following Administration of a Single 20 mg/0.625 mg Dose of BZA/ CE (Formulation A reference, PCP and Formulation C, test, PNP)

Analyte	C_{max}	AUC_T	AUC
Unconjugated estrone	99 (91-108)	100 (95-105)	101 (94-109)
Unconjugated estrone adjusted for baseline	95 (85-107)	96 (88-106)	94 (84-105)
Unconjugated equilin	93 (85-102)	90 (79-104)	-
Total estrone	96 (89-104)	99 (93-104)	101 (95-106)
Total estrone adjusted for baseline	93 (86-101)	95 (89-102)	95 (89-102)
Total equilin	100 (92-110)	105 (96-114)	105 (97-114)
Bazedoxifene	78 (68-91)	70 (62-80)	74 (66-83)

Conclusions:

This study is a repeat of Study 114 in which formulations A and C were shown to be not BE. Study 114 showed that formulation C had lower exposure (Cmax was 16% and AUC was 22%) than formulation A. The difference between the two studies is that the current study was conducted as partial replicate to assess the intra-subject variability.

Similar to Study 114, the 90% CI for BZA data were outside the range of 80% to 125% for both Cmax and AUC. The Cmax of BZA for PNP formulation (test, Formulation C) was approximately 22% lower than the reference formulation (PCP, Formulation A). Similarly, the AUC for Formulation C (PNP) was approximately 26% lower than Formulation A (PCP). Therefore, it can be concluded that the two formulations are not BE. As in Study 114, formulation C produces lower BZA exposure than formulation A in the range of 22% for Cmax and to 26% for AUC.

Reference ID: 3319979

Study 1121-US (20/0.0.625, Formulation A and Formulation C, Steady-State):

Title: "An Open-label, Randomized, Multicenter Study to Compare Bazedoxifene Steady-State Exposures Obtained with 2 Bazedoxifene Acetate/Conjugated Estrogen Formulations in Postmenopausal Women"

Objectives: The primary objective of the study was to document subject exposure to BZA from 1 of 2 formulations of BZA 20 mg/CE 0.625 mg **after steady-state administration**.

The secondary objective of the study was to obtain additional safety and tolerability data concerning BZA/CE in postmenopausal women.

Rationale:

The term Premarin Current Process (PCP, Formulation A) refers to the (b) (4) BZA/CE combination tablets used in the earlier phase 1, 2, and 3 studies. The purpose of this study was to determine the BE of BZA/CE combination tablets having the PCP (b) (4) with BZA/CE combination tablets having a reformulated Premarin New Process (PNP, Formulation C) (b) (4)

Design:

This was an open-label, randomized, parallel, inpatient/outpatient study design with **14 days** drug administration. Subjects received 1 of 2 formulations: Premarin current process (PCP, formulation A) and Premarin new process (PNP, formulation C). In both cases, the subjects received an oral tablet with BZA 20 mg/CE 0.625 mg.

Subjects were received BZA/CE and Caltrate + D tablets, which contained 600 mg calcium and 200 IU vitamin D, once daily, orally for 14 days. On days 1 through 12, subjects were permitted to self-administer their test article with or without a meal, and were instructed to be consistent in their regimen throughout this period. On day 13, subjects were admitted for an overnight confinement for steady-state PK sampling after the day 14 dose. On day 14, subjects were administered test article by site staff according to their regimen, with or without a meal, as established by the prior 12 days.

Treatment A: Once daily (QD) dose for 14 days (Day 1 through Day 14) of BZA/CE 20 mg/0.0.625 mg tablet (PNP) tablet
(Test **Formulation C**)

Treatment B: Once daily (QD) dose for 14 days (Day 1 through Day 14) of BZA/CE 20 mg/0.625 mg tablet (PCP) tablet
(Reference **Formulation A**)

The formulations used in this study are listed below in **Table 1121-1**.

Table 1121-1. Formulations Tested in Study 1121-US:

Drug Product	Strength (mg)	Dosage Form	Batch Number
BZA/CE (PCP)	20.0/0.625	Tablet	2002B0199
BZA/CE (PNP)	20.0/0.625	Tablet	W92631A

Blood Samples:

Blood samples for BZA/CE PK analysis were collected at adequate intervals over 24 hours.

Results:

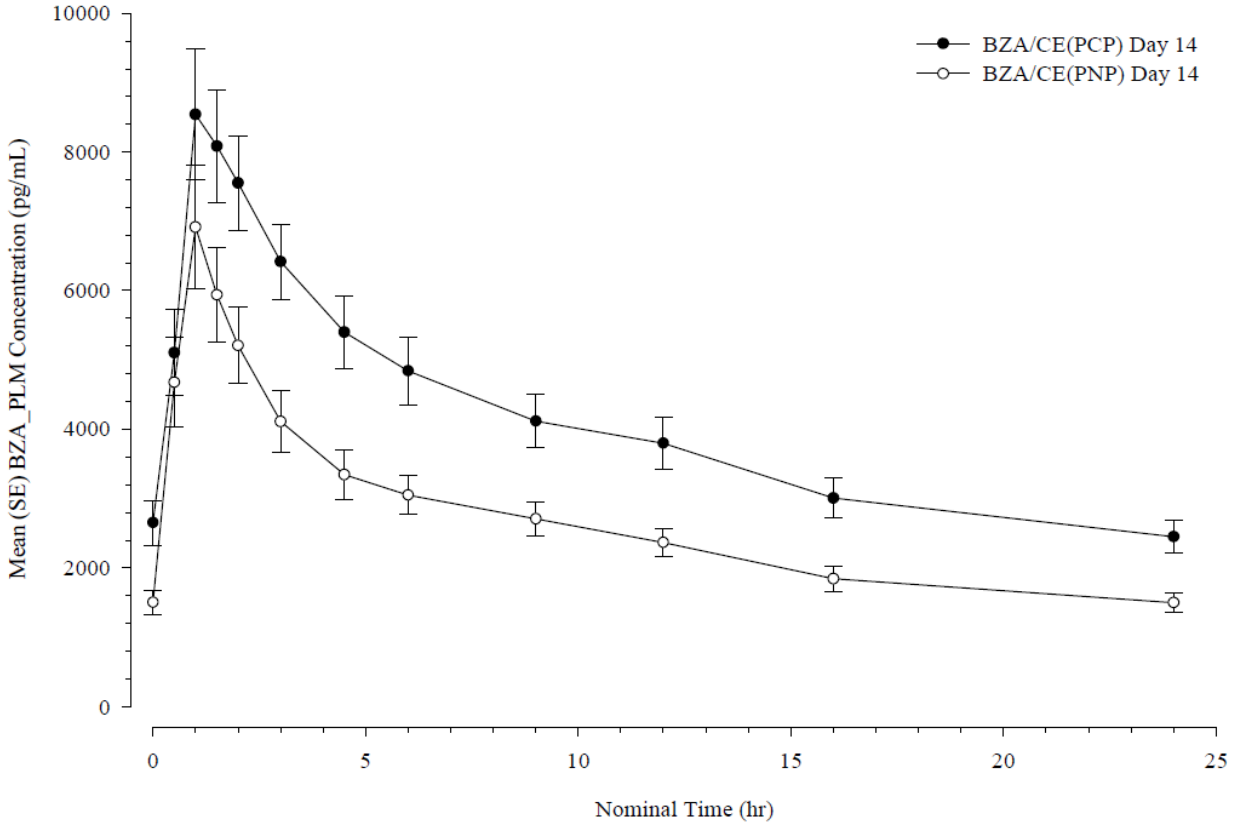
The focus of this study is on the PK of BZA. **Table 1121-2** shows the summaries of BZA PK and statistical data.

Table 1121-2. PK Parameter Estimates of BZA Following Administration of a 20 mg/0.625 mg Dose of BZA/CE Once Daily for 14 days

Mean ± SD (CV%) (Geometric Mean)	Treatment	
	BZA/CE (PCP) n=33	BZA/CE (PNP) n=35
C_{max} (ng/mL)	10.80 ± 4.53 (42) [9.84]	7.96 ± 4.74 (60) [6.72]
t_{max} (h)	1.00 (0.50 , 6.00)	1.50 (0.53 , 12.00)
$t_{1/2}$ (h)	18.90 ± 7.82 (41) [17.72]	19.82 ± 15.45 (78) [17.52]
AUC_T (ng*h/mL)	97.25 ± 47.66 (49) [86.85]	63.15 ± 34.30 (54) [55.68]
AUC_{ss} (ng*h/mL)	97.25 ± 47.66 (49) [86.85]	63.15 ± 34.29 (54) [55.69]
C_{min} (ng/mL)	2.21 ± 1.29 (58) [1.89]	1.33 ± 0.88 (66) [1.06]
C_{ave} (ng/mL)	4.05 ± 1.99 (49) [3.62]	2.63 ± 1.43 (54) [2.32]
FI (%)	237 ± 116 (49) [212]	266 ± 147 (55) [230]

Reference ID: 3319979

Figure 1121-1. Mean BZA Plasma-Concentrations Time Profiles Following Administration of a 20 mg/0.625 mg Dose of BZA/CE: PCP (Formulation A, and PNP Formulation C) Once Daily for 14 Days



Conclusions:
This study is a repeat of Studies 114 and 1120 in which formulations A and C were shown to be not BE. In study 1120, Formulation C had lower exposure (16 to 26%) than Formulation A. The difference between the previous two studies is that the current study was conducted after multiple doses to reach steady state.

Similar to Studies 114 and 1120, study 1121 demonstrated that formulation C (PNP) was lower exposure than that from formulation A. The Cmax of formulation C was **32%** and the AUC was **36%** lower than that of formulation A at steady state.

Therefore, it can be concluded that the two formulations are **not BE**.

Study 1116-US (Effect of Food, 20/0.45 and 20/0.625) (Formulation C):

Title: "An Open-Label, Single-Dose, Crossover Study to Determine the Effect of a High-Fat Meal on the Relative Bioavailability and Pharmacokinetics of a Single Dose of Bazedoxifene Acetate/Conjugated Estrogens (Premarin® New Process) Administered Orally to Healthy Postmenopausal Women"

Objectives: The primary objective of this study was to determine the effect of a high-fat meal on the BA and PK of a single oral dose of the BZA 20 mg/CE 0.625 mg (PNP) tablet formulation, assessing both the BZA and the CE components.

The secondary objective for this study was to obtain information on the PK of the BZA 20 mg/CE 0.45 mg (PNP) tablet formulation in healthy postmenopausal women.

The third objective was to obtain additional safety and tolerability data concerning the BZA/CE (PNP) compound in healthy postmenopausal women.

Rationale:

This was a BA and food-effect study that examined a new formulation of BZA/CE tablets having a reformulated Premarin® New Process (PNP) (b) (4)

Design:

This was an open-label, single-dose, randomized-to-sequence, 3-period, crossover, inpatient/outpatient study conducted in 23 healthy postmenopausal women. The first 2 periods constituted the food effect portion of the study and subjects were given the BZA 20 mg /CE 0.625 mg (PNP) tablet in a fasting or fed state according to a randomized sequence. In the third period, all subjects were given the BZA 20 mg/CE 0.45 mg (PNP) strength tablet in a fasting state. There was a 10-day washout between each of the following three treatments:

Treatment A (Fasting):	Single dose of BZA/CE (PNP) 20mg/0.625 mg administered under **fasting** conditions
Treatment B (Fed):	Single dose BZA/CE (PNP) 20mg/0.625 mg administered 5 minutes after completion of the FDA recommended **high-fat breakfast**
Treatment C (Fasting):	Single dose BZA/CE (PNP) 20mg/0.45 mg administered under **fasting** conditions

The randomized crossover design was selected for the food-effect portion because it compares the PK effects in both fasting and fed states within subjects using the intra-subject variability instead of comparing between subjects using the total (intra-subject plus inter-subject) variability. The third period allowed characterization of the PK parameters at the lower dose of CE. No control groups were used in this study.

The formulations used in this study are listed below in **Table 1116-1**.

Table 1116-1. Formulations Tested in Study 1116-US:

Drug Product	Strength	Dosage Form	Formulation Number	Batch Number
BZA/CE (PNP)	20mg/0.625 mg	Tablets	0932315C	W92812A
BZA/CE (PNP)	20mg/0.45 mg	Tablets	0932313C	W92846A

Blood Samples:

Blood samples for BZA/CE PK analysis were collected at adequate intervals over 96 hours.

Results:

The focus of this study is on the PK of BZA. The BZA PK data are summarized in **Tables 1116-2 and 3** and **Figure 1116-1.**

Table 1116-2. BZA PK Parameters after Administration of BZA 20 mg/CE 0.625 mg under Fasting and Fed Conditions

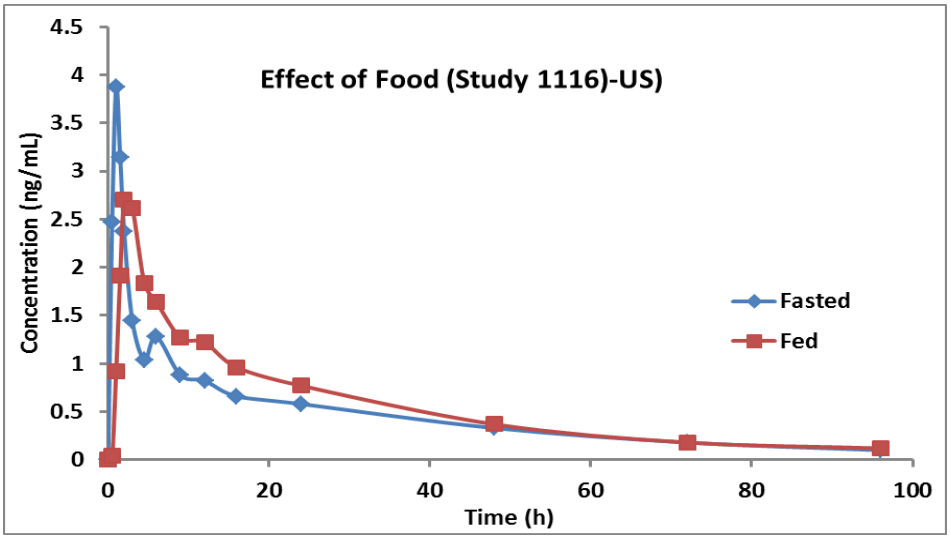
Treatment		**C_{max} (ng/mL)**	**t_{max} (h)**	**$t_{1/2}$ (h)**	**AUC_T (ng·h/mL)**	**AUC (ng·h/mL)**
1 BZA 20 mg/ CE 0.625 mg Tablet (Fasting)	Mean±SD	4.25±2.48	1.4±1.0	28.8±8.6	43.7±21.9	48.2±24.3
	%CV	58.3	74.3	29.9	50.0	50.4
	N	23	23	23	23	23
	Geometric Mean	3.26	1.2	27.6	38.2	42.3
	(Range)	(0.37-8.43)	(0.5-4.5)	(18.1-49.7)	(12.3-107)	(13.8-118)
1 BZA 20 mg/ CE 0.625 mg Tablet (Fed)	Mean±SD	4.12±3.34	3.4±2.3	26.2±5.8	53.0±25.1	57.6±26.1
	%CV	81.0	68.4	22.0	47.3	45.4
	N	23	23	23	23	23
	Geometric Mean	3.26	2.9	25.7	48.5	52.8
	(Range)	(1.00-14.2)	(1.0-12.0)	(18.8-38.8)	(21.0-131)	(22.6-135)
p-Values of Fixed Effects from the Mixed-Effects Model of Log-Transformed Pharmacokinetic Parameters						
Source of Variation						
Sequence		0.381	0.600	0.792	0.007	0.010
Treatment		0.998	<0.001	0.101	0.128	0.134
Period		0.889	0.499	0.922	0.848	0.836
Statistical Power (%)		13.2	24.9	-	29.5	32.3
GLS Means Ratio and CLs[a]						
GLS Means Ratio		100	247	-	127	125
90% CL		64-156	186-329	-	98-164	98-159

Reference ID: 3319979

Table 1116-3. BZA Pharmacokinetic Parameters after Administration of BZA 20 mg/CE 0.45 mg under a Fasting Condition

Treatment		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1 BZA 20 mg/ CE 0.45 mg Tablet	Mean±SD	4.34±2.80	1.6±1.5	28.6±9.2	40.6±20.7	45.0±22.6
	%CV	64.5	89.3	32.3	51.1	50.3
	N	23	23	23	23	23
	Geometric Mean	3.26	1.3	27.3	34.1	38.1
	(Range)	(0.43-12.2)	(1.0-6.0)	(16.6-52.1)	(6.6-78.5)	(7.7-85.3)

Figure 1116-1. Mean BZA Plasma Concentrations-Time Profiles Following Administration of a Single 20 mg/0.625 mg Dose of BZA/CE (PNP) under Fasting and Fed Conditions (Study 1116-US)



Conclusions:

The BA of BZA from a BZA 20 mg/CE 0.625 mg tablet was greater when the tablet was administered following a high-fat breakfast than when administered to fasting subjects. The mean Cmax of BZA was slightly reduced when taken with food, but AUC was approximately 27% greater. In addition, the administration of BZA/CE after a high-fat breakfast delayed the tmax of BZA to 3.4 hours compared with 1.4 hours in the fasting subjects.

In contrast to the differences observed with BZA, food appeared to have little effect on the PK of the estrogens. For both total and unconjugated estrone and equilin, the extent of absorption (AUC) was comparable between the fed and the fasting subjects.

In conclusion, food appeared to have a modest effect on the extent, and rate of absorption of BZA from BZA 20 mg/CE 0.625 mg combination tablets. In contrast, food had little effect on the PK of the CE, with slight decreases in Cmax and AUC.

Study 3068A1-111-EU (Absolute Bioavailability of BZA, Monotherapy):

Title: " Absolute/Relative Bioavailability of BZA in Healthy Postmenopausal Women"

Objectives: The primary objective was to assess the absolute BA of 2 oral formulations (tablet and capsule) of BZA with respect to an IV formulation in healthy postmenopausal women.

The secondary objectives were first to assess the relative oral BA of BZA after administration of tablet and capsule formulations in healthy postmenopausal women and then to assess the safety of each formulation.

Design:

This was a randomized, open-label, single-dose, 3-period crossover, inpatient and outpatient study performed with 18 healthy postmenopausal women. The study was conducted at a single site. Each study period consisted of a 36-hour (2 nights and 1 day) inpatient phase followed by 6 outpatient visits. There was a washout interval of at least 2 weeks between doses administered. Each subject fasted overnight was assigned to receive the treatments below in a random order:

Treatment A: One 10-mg tablet of BZA with 240 mL of room-temperature water.
Treatment B: Two 5-mg capsules of BZA with 240 mL of room-temperature water.
Treatment C: One 3-mg IV dose of BZA. BZA acetate was provided (b) (4)

The formulations used in this study are listed below in **Table 3068A1-1**.

Table 3068A1-1. Formulations Tested in Study 3068A1-111-EU:

Test Article	Strength (Units)	Batch Number	Source
Treatment A, bazedoxifene	10 mg	2000B0288	Tablet
Treatment B, bazedoxifene	5 mg	1997B0169	Capsule
Treatment C, bazedoxifene	3 mg	1999B0095	Vial, (b) (4)
	10 mL	1999B0101	Vial

Blood Samples:

Blood samples for BZA PK analysis were collected at adequate intervals over 168 hours (over 8 days).

Reference ID: 3319979

Results:

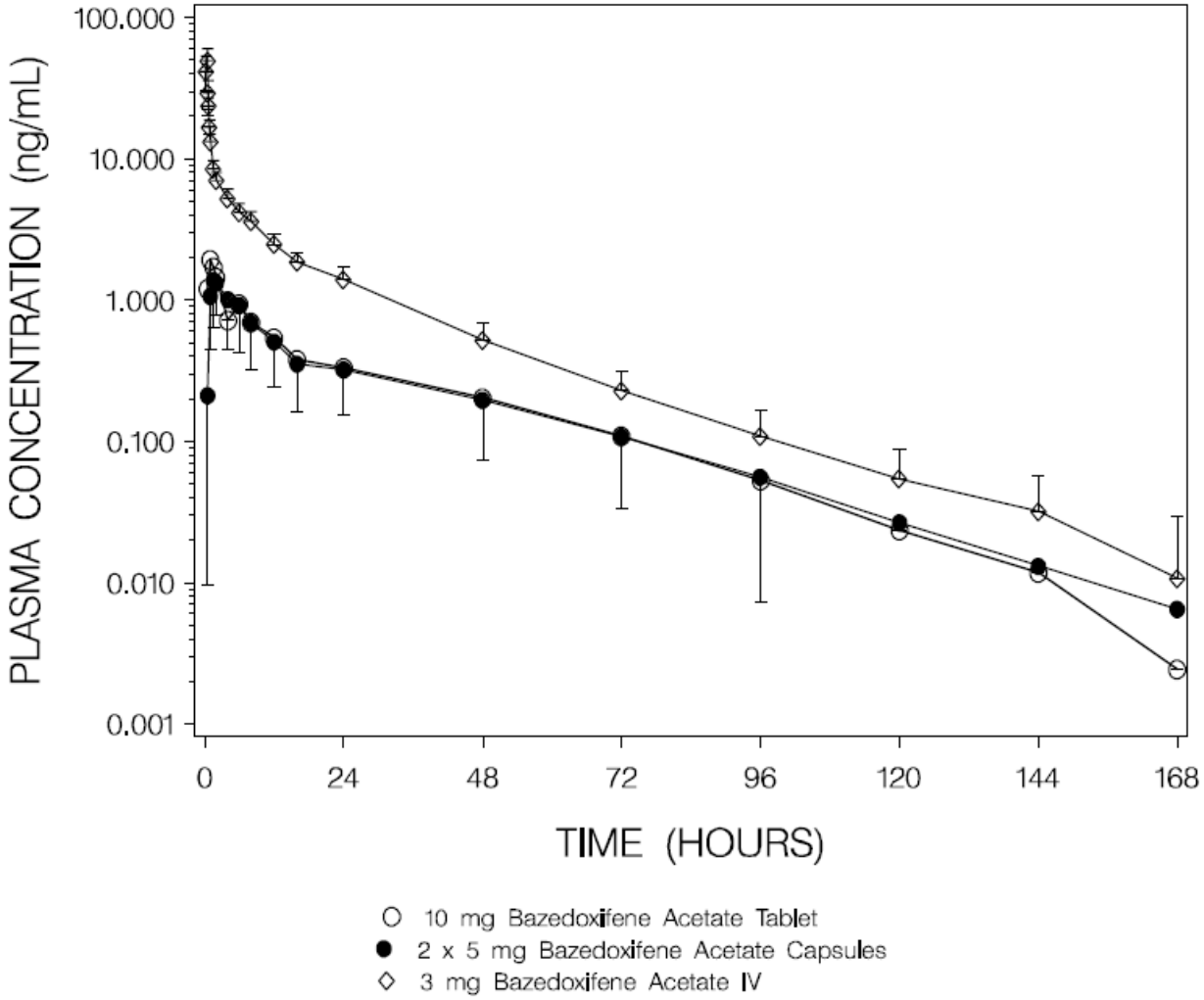
Based on this study, the absolute BA from both capsule and tablet is 6.2% (**Table 3068A1-2 and Figure 3068A1-1).**

Table 3068A1-2. BZA PK Parameters after Administration of Oral Tablet and Capsules Compared to Intravenous Administration (Study 3068A1)

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)	Cl/F (L/h/kg)	F (%)
10-mg tablet							
Mean ± SD	2.1 ± 0.7	1.5 ± 1.2	30 ± 7	28 ± 15	29 ± 14	6.6 ± 2.5	6.2 ± 2.1
CV, %	31.9	77.3	23.6	52.4	48.9	37.5	33.4
Geometric Mean	2.0	1.3	29	25	27	6.1	5.9
Min	0.8	1.0	18	9	14	2.6	3.4
Max	3.8	6.0	45	60	62	11.9	10.1
2x5-mg capsules							
Mean ± SD	1.7 ± 0.6	2.3 ± 1.3	30 ± 8	27 ± 13	29 ± 13	6.7 ± 2.7	6.2 ± 2.3
CV, %	35.0	57.9	27.0	47.1	43.8	39.5	37.7
Geometric Mean	1.6	2.0	29	24	26	6.2	5.8
Min	0.8	1.0	17	10	12	2.7	3.0
Max	3.2	6.0	46	63	64	11.8	12.6
3 mg IV							
Mean ± SD	51.2 ± 11.7	0.5 ± 0.1	28 ± 6	137 ± 23	138 ± 23	0.4 ± 0.1	100.0 ± 0.0
CV, %	22.8	17.1	21.8	16.5	16.5	18.2	0.0
Geometric Mean	49.9	0.5	27	135	136	0.4	100.0
Min	36.2	0.3	19	95	97	0.3	100.0
Max	74.1	0.5	38	183	185	0.5	100.0
p-Values From Log-Transformed Analysis of Variance for a 2-Period Crossover Design (Tablet vs Capsule)							
Sequence	0.57	0.52	0.21	0.61	0.58	0.76	0.79
Subject within Sequence	0.05	0.56	0.36	0.001	0.001	0.001	0.001
Treatment	0.02	0.02	0.90	0.85	0.80	0.80	0.80
Period	0.69	0.64	0.23	0.22	0.30	0.30	0.30

Treatment	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)	Cl/F (L/h/kg)	F (%)
Geometric Mean Ratio and Ordinary Confidence Limits (Tablet vs Capsule)							
Statistical Power	53	18	-	73	74	74	-
Least Squares Mean Ratio (%)	80	152	-	99	98	102	-
90% confidence interval	69-93	114-204	-	88-111	88-110	91-114	-

Figure 3068A1-1. Mean BZA Plasma Concentration-Time Profiles After Administration of Oral Tablet and Capsules Compared to Intravenous Administration (Study 3068A1)



Conclusions:

This study was reviewed [redacted] (b) (4) [redacted] (b) (4)
Since there were several changes in the formulation over the years, the absolute BA of BZA is anticipated to be also low (i.e., <10%) or comparable with the final-to-be marketed formulation proposed in this NDA.

Based on the low BA of BZA, it is anticipated that intrinsic and/or extrinsic factors may affect and potentially increase the rate and extent of BZA absorption. Considering the narrow therapeutic index of BZA, the factors that may potentially affect the rate and extent of BZA absorption pose safety and/or efficacy concerns.

Study 3115A1-1136-US (Relative Bioavailability BZA/CE vs BZA Tablet):

Title: "An Open-Label, Single-Dose, Randomized, 2 –period, Crossover, Relative Bioavailability Study of a Bazedoxifene Acetate/Conjugated Estrogens Tablet Compared With a Bazedoxifene Tablet in Healthy, Postmenopausal Women"

Objectives: The primary objective was to compare the BA of one BZA/CE 20 mg/0.45 mg tablet with one BZA 20 mg tablet, assessing the BZA component.

The secondary objective was to obtain additional safety and tolerability data concerning both BZA/CE and BZA in healthy, postmenopausal women.

Design:

This was a single-dose, randomized, open-label, 2-period, 2-treatment, crossover, inpatient/outpatient study in 24 healthy, postmenopausal subjects. There was at least a 10-day washout between each single dose administration. Subjects fasted overnight for at least 10 hours and randomly assigned to receive the following treatments:

Treatment A (Test): Single dose of BZA/CE 20mg/0.45 mg tablet
Treatment B (Reference): Single dose BZA tablet 20 mg

The formulations used in this study are listed below in **Table 1136-1**.

Table 1136-1. Formulations Tested in Study 3115A1-1136-US:

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA/CE (test)	20/0.45	Tablet	0932557C	D87931
BZA (reference)	20	Tablet	0931958C	C87519

Blood Samples:

Blood samples for BZA/CE PK analysis were collected at adequate intervals over 96 hours.

Results:

The focus of this study is on the PK of BZA. The BZA PK data are summarized in **Table 1136-2.**

Reference ID: 3319979

Table 1136-2. BZA PK Parameters Following Administration of a Single Dose of 20 mg BZA and a Single Dose of 20/0.45 mg BZA/CE (Study 1136-US).

Mean ± SD	Treatment	
	BZA 20 mg	BZA 20 mg + CE 0.45 mg
N	24	24
C_{max}(ng/mL)	3.14 ± 1.25	4.69 ± 2.42
t_{max}[a] (hr)	1.00 (0.50 - 6.00)	1.00 (0.50 - 3.00)
$t_{1/2}$ (hr)	25.53 ± 8.08	24.61 ± 6.65
AUC_T (ng•hr/mL)	62.1 ± 30.1	66.3 ± 25.8
AUC (ng•hr/mL)	68.3 ± 33.4	72.6 ± 30.6

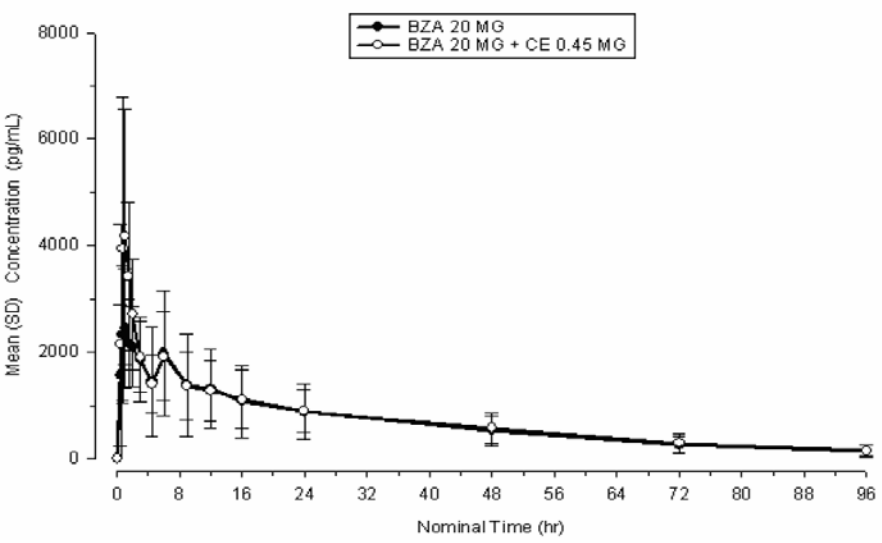
a. Median (Min - Max).

Table 1136-3. Statistical Summary of BZA PK Parameters Following Administration of a Single Dose of 20 mg BZA and a Single Dose of 20/0.45 mg BZA/CE (Study 1136-US).

	p-Values from Log-Transformed Analysis of Variance		
	C_{max}	AUC_T	AUC
Factor	(ng/mL)	(ng•hr/mL)	(ng•hr/mL)
Period	0.0906	0.270	0.263
Sequence	0.0541	0.974	0.978
Treatment	0.00189	0.231	0.279
Intersubject CV%	24.6	34.3	37.0
Intrasubject CV%	34.5	27.3	26.9
	Pair-wise Comparison: BZA 20 mg + CE 0.45 mg (Test) vs. BZA 20 mg (Ref)		
Ratio of Least Square Geometric Means (%)	141	110	109
90% Confidence Interval around Ratio	119-166	96-126	95-124
Probability < 80%	0.00000362	0.000230	0.000278
Probability > 125%	0.883	0.0569	0.0417
Total Probability (<80%,>125%)	0.883	0.0571	0.0420
Statistical Power (%)	71.8	87.1	88.0

Reference ID: 3319979

Figure 1136-1. Mean Concentration-Time Profiles for Following Administration of a Single Dose of 20 mg BZA and a Single Dose of 20/0.45 mg BZA/CE (Study 1136-US).



Conclusions:

The results show that the adjusted geometric mean ratio (90% CI) of AUC for BZA was 109% (95%, 124%) which was within BE limits (80%, 125%), but Cmax was approximately 41% higher with the combination tablet compared with the monotherapy tablet. Tmax and t½ were comparable between the 2 products.

B. Clinical Pharmacology Studies

Study 3115A1-101-US

Title: "A Study to Assess the Potential Pharmacokinetics Interaction Between TSE-424 and Conjugated Estrogens in Healthy Postmenopausal Women."

Objective: The objective of the study was to assess the potential PK interaction between BZA (previously referred to as TSE-424) and CE in healthy postmenopausal women.

Methods: This was a single site, open-label, single-dose, 3-treatment, 3-period, randomized, crossover study in healthy postmenopausal women age 35 to 65 yrs, inclusive.

Treatment Groups

Treatment Group	Study Medication
A	CE 0.625 mg
B	Bazedoxifene 40 mg
C	Bazedoxifene 40 mg/CE 0.625 mg

Test Products

Dosage Form	Batch Number	Formulation Number
Bazedoxifene 40 mg/CE 0.625 mg [a,b]	2001B0014	0931493C
Bazedoxifene 40 mg[a]	2001B0007	0931422C
CE 0.625 mg[b]	W90352A	0929535B

Abbreviations: CE = conjugated estrogens
a: Product manufactured at Wyeth Research, Montreal, Quebec, Canada
b: Product manufactured at Wyeth Pharmaceuticals Co., Guayama, Puerto Rico

Each subject received a single oral dose of 1 of 3 treatments during each study period. There was at least a 21-day washout interval between treatments. A single oral dose of study medication was administered with 240 mL of room temperature water at approximately 8 am after a 10-hr overnight fast (no food or fluids). Subjects continued to abstain from food and fluids until 4 hrs post-dose. Room temperature or cold water was permitted as needed beginning 2 hrs postdose. Subjects refrained from lying down or engaging in strenuous exercise until 5 hrs after drug administration. Subjects remained at the study site until Day 3 of each study period. Subjects returned to the study site for 2 outpatient visits on Days 4 and 5 for vital sign assessments, adverse event and concomitant treatment monitoring, and PK blood sampling.

Baseline Estradiol and Estrone Concentrations
There were three blood samples taken for determination of baseline estradiol and estrone concentrations. Subjects reported to the study site at about 7 am for 2 consecutive days (Days -2 and -1) before each study period for baseline time points (approximately -48 and -24 hrs) and predose (at 0 hr).

Plasma concentrations were adjusted for baseline by subtracting the baseline value.

Pharmacokinetic Sampling: For plasma concentrations of unconjugated and total (unconjugated plus conjugated) estrone, equilin, 17β-estradiol, 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-

Reference ID: 3319979

dehydroestradiol, blood samples were taken -0.5, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 72 and 96 hrs postdose on Day 1. For BZA plasma concentrations, blood samples were taken at -0.5, 0.5, 1, 1.5, 2, 4.5, 6, 9, 12, 24, 48, 72, and 96 hrs postdose on Day 1.

Results:
The following table summarizes the geometric least squares mean ratios (90% CI) for various estrogens following a single dose of BZA 40 mg/CE 0.625 mg compared with BZA 40 mg alone or CE 0.625 mg alone (sponsor's table 10.0-1, section 10).

Analyte	C_{max}	t_{max}	AUC_T	AUC
Unconjugated estrone	91 (84-99)	102 (76-138)	94 (86-102)	100 (86-117)
Unconjugated estrone adjusted for baseline	86 (76-97)	102 (76-138)	79 (65-97)	75 (57-100)
Unconjugated equilin	97 (90-105)	120 (103-139)	106 (83-133)	110 (76-159)
Unconjugated 17β-estradiol	93 (86-101)	103 (82-129)	94 (79-111)	98 (82-117)
Unconjugated 17β-estradiol adjusted for baseline	81 (71-94)	103 (82-129)	71 (55-92)	70 (50-97)
Unconjugated 17β-dihydroequilin	96 (88-104)	112 (92-136)	88 (72-107)	92 (77-110)
Total estrone	80 (69-93)	104 (84-129)	94 (87-102)	90 (82-99)
Total estrone adjusted for baseline	79 (67-93)	104 (84-129)	90 (80-101)	88 (76-101)
Total equilin	82 (72-94)	117 (95-145)	92 (82-103)	91 (82-102)
Total 17β-estradiol	86 (72-103)	101 (85-119)	94 (86-104)	94 (84-105)
Total 17β-estradiol adjusted for baseline	86 (72-103)	101 (85-119)	92 (81-104)	91 (80-104)
Total 17β-dihydroequilin	82 (71, 94)	105 (81, 136)	89 (79, 101)	96 (84, 110)
Total $\Delta^{8,9}$-dehydroestrone	89 (82-96)	124 (113-137)	92 (84-101)	92 (82-105)
Total 17β-$\Delta^{8,9}$-dehydroestradiol	83 (73-94))	110 (90-135)	86 (75-98)	88 (78-100)
Bazedoxifene	126 (103-153)	87 (72-104)	123 (110-138)	124 (110-140)

a: Ratio of bazedoxifene 40 mg/CE 0.625 mg combination tablet to CE 0.625 mg or bazedoxifene 40 mg tablet alone (%).

The following table is a summary of PK parameters for Unconjugated Estrone (sponsor's table 8.1-1, section 8.1).

Reference ID: 3319979

Treatment	Parameter	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
CE 0.625 mg	Mean ± SD	77.2 ± 36.0	15.6 ± 20.2	91.3 ± 88.4	3466 ± 1405	6538 ± 3242
	CV, %	46.6	129.6	96.8	40.5	49.6
	Geometric mean	69.3	11.6	74.5	3204	5826
	Range	22.2-144.0	6.0-96.0	27.0-439.8	1527-6243	2675-14933
BZA 40 mg/CE 0.625 mg	Mean ± SD	67.8 ± 27.2	12.7 ± 6.8	88.5 ± 45.1	3289 ± 1306	6338 ± 2931
	CV, %	40.1	53.4	51.0	39.7	46.2
	Geometric mean	62.9	11.8	78.8	3024	5777
	Range	29.9-120.0	7.5-40.0	37.6-206.2	954-578	2747-12921
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.81	0.51	0.65	0.31	0.10
Treatment		0.07	0.89	0.48	0.22	0.96
Period		0.13	0.44	0.06	0.06	0.49
Statistical power		99	24	...	99	68
GLS mean ratio (%)[a]		91	102	...	94	100
90% Log-transformed CI [a]		84-99	76-138	...	86-102	86-117

The following table is a summary of PK parameters for Baseline-Adjusted Unconjugated Estrone (sponsor's table 8.2-1, section 8.2).

Treatment	Parameter	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
CE 0.625 mg	Mean ± SD	57.9 ± 31.9	15.6 ± 20.2	25.2 ± 20.9	1634 ± 885	2005 ± 1308
	CV, %	55.1	129.6	82.7	54.2	65.3
	Geometric mean	49.1	11.6	21.1	1404	1637
	Range	10.5-122.3	6.0-96.0	10.6-104.7	459-3690	526-5080
BZA 40 mg/CE 0.625 mg	Mean ± SD	47.1 ± 21.6	12.7 ± 6.8	19.6 ± 7.1	1339 ± 734	1484 ± 828
	CV, %	45.9	53.4	36.0	54.8	55.8
	Geometric mean	42.1	11.8	18.6	1114	1233
	Range	16.3-82.0	7.5-40.0	12.7-34.0	347-2861	381-3161
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.97	0.51	0.37	0.77	0.68
Treatment		0.04	0.89	0.41	0.07	0.09
Period		0.25	0.44	0.95	0.46	0.49
Statistical power		86	24	-	43	26
GLS mean ratio (%)[a]		86	102	-	79	75
90% Log-transformed CI [a]		76-97	76-138	-	65-97	57-100

The following table is a summary of PK parameters for Unconjugated Equilin (sponsor's table 8.3-1, section 8.3).

Treatment	Parameter	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
CE 0.625 mg	Mean ± SD	27.0 ± 13.6	8.3 ± 3.5	11.1 ± 5.2	404 ± 395	616 ± 369
	CV, %	50.3	42.2	46.8	97.8	59.9
	Geometric mean	26.1	8.4	10.1	296	553
	Range	0.0-52.5	0.0-16.0	4.7-22.1	59-1546	338-1751
BZA 40 mg/CE 0.625 mg	Mean ± SD	23.7 ± 11.2	9.1 ± 3.6	24.8 ± 47.6	375 ± 255	873 ± 1147
	CV, %	47.3	39.8	192.3	67.9	131.3
	Geometric mean	25.5	10.0	13.1	318	600
	Range	0.0-44.8	0.0-14.0	4.0-200.8	117-1224	177-4982
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.29	0.81	0.79	0.38	0.84
Treatment		0.51	0.05	0.29	0.69	0.59
Period		0.01	0.96	0.67	0.21	0.61
Statistical power		100	69	-	35	16
GLS mean ratio (%)[a]		97	120	-	106	113
90% Log-transformed CI[a]		90-105	103-139	-	83-133	77-165

The following table is a summary of PK parameters for Unconjugated 17β-Estradiol (sponsor's table 8.4-1, section 8.4).

Treatment	Parameter	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
CE 0.625 mg	Mean ± SD	12.0 ± 4.9	15.4 ± 7.0	70.7 ± 50.2	630 ± 326	1210 ± 1057
	CV, %	41.3	45.6	71.0	51.8	87.3
	Geometric mean	11.1	14.2	61.6	540	966
	Range	4.7-22.1	6.0-32.0	24.7-262.5	135-1224	312-5115
BZA 40 mg/CE 0.625 mg	Mean ± SD	11.3 ± 4.9	15.5 ± 6.8	72.3 ± 38.8	601 ± 335	1127 ± 662
	CV, %	43.5	44.1	53.7	55.7	58.7
	Geometric mean	10.4	14.6	63.4	508	943
	Range	5.2-20.9	9.0-40.0	26.9-157.0	172-1236	306-2462
	p-Values From Log Transformed Analysis of Variance					
Sequence		0.91	0.41	0.44	0.28	0.15
Treatment		0.14	0.85	0.73	0.50	0.82
Period		0.01	0.98	0.90	0.18	0.27
Statistical power		99	36	-	59	53
GLS mean ratio (%)[a]		93	103	-	94	98
90% Log-transformed CI[a]		86-101	82-129	-	79-111	82-117

The following table is a summary of PK parameters for Baseline-Adjusted Unconjugated 17β-Estradiol (sponsor's table 8.5-1, section 8.5).

Treatment	Parameter	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
CE 0.625 mg	Mean ± SD	9.15 ± 4.21	15.4 ± 7.0	29.2 ± 12.3	360 ± 200	468 ± 296
	CV, %	46.0	45.6	42.2	55.4	63.3
	Geometric mean	8.44	14.2	27.1	314	401
	Range	4.68-21.70	6.0-32.0	14.1-64.3	135-935	153-1413
BZA 40 mg/CE 0.625 mg	Mean ± SD	7.68 ± 3.55	15.5 ± 6.8	32.4 ± 21.3	264 ± 144	349 ± 182
	CV, %	46.2	44.1	65.8	54.6	52.1
	Geometric mean	6.94	14.6	27.3	225	295
	Range	3.17-15.15	9.0-40.0	10.4-85.8	46-605	51-796
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.78	0.41	0.10	0.65	0.27
Treatment		0.02	0.85	0.84	0.03	0.07
Period		0.05	0.98	0.08	0.16	0.28
Statistical power		72	36	-	29	23
GLS mean ratio (%)[a]		81	103	-	71	72
90% Log-transformed CI[a]		71-94	82-129	-	55-92	53-97

The following table is a summary of PK parameters for Unconjugated 17β-Dihydroequilin (sponsor's table 8.6-1, section 8.6).

Treatment	Parameter	C_{max} (pg/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (pg·h/mL)	AUC (pg·h/mL)
CE 0.625 mg	Mean ± SD	25.8 ± 12.2	9.9 ± 4.4	14.9 ± 9.2	478 ± 328	677 ± 347
	CV, %	47.5	44.2	61.9	68.5	51.3
	Geometric mean	22.9	9.2	13.4	390	613
	Range	5.3-59.5	4.5-24.0	8.4-48.9	62-1312	324-1563
BZA 40 mg/CE 0.625 mg	Mean ± SD	23.7 ± 8.7	10.4 ± 2.1	14.3 ± 4.3	434 ± 264	613 ± 272
	CV, %	36.7	20.5	29.9	60.9	44.3
	Geometric mean	21.9	10.2	13.8	341	562
	Range	6.8-40.4	7.5-16.0	9.2-25.6	23-1140	233-1307
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.75	0.63	0.83	0.76	0.36
Treatment		0.36	0.32	0.86	0.26	0.44
Period		0.008	0.64	0.70	0.25	0.33
Statistical power		99	47	-	46	51
GLS mean ratio (%)[a]		96	112	-	88	92
90% Log-transformed CI[a]		88-104	92-136	-	72-107	77-110

Unconjugated $\Delta^{8,9}$-Dehydroestrone - in all subjects only 3 concentrations were above the LLOQ of 5 pg/mL; therefore, no statistical comparisons were performed and no PK parameters reported.

Unconjugated 17β-$\Delta^{8,9}$-Dehydroestradiol

The following table is a summary of PK parameters for Total Estrone (sponsor's table 8.9-1, section 8.9).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	2.95 ± 1.76	9.4 ± 4.4	47.9 ± 18.7	66.0 ± 37.1	91.8 ± 59.1
	CV, %	59.7	46.6	39.0	56.2	64.4
	Geometric mean	2.50	8.7	44.6	58.0	76.7
	Range	0.52-8.42	4.5-24.0	21.4-94.9	21.0-186.8	26.6-254.3
BZA 40 mg/CE 0.625 mg	Mean ± SD	2.26 ± 1.07	9.4 ± 2.4	46.3 ± 16.1	60.4 ± 29.3	79.2 ± 44.2
	CV, %	47.5	25.8	34.7	48.5	55.8
	Geometric mean	2.00	9.1	43.7	54.4	69.4
	Range	0.57-5.04	6.0-16.0	27.4-79.4	19.6-147.2	23.2-211.7
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.48	0.04	0.10	0.60	0.43
Treatment		0.02	0.74	0.54	0.20	0.08
Period		0.18	0.93	0.06	0.16	0.11
Statistical power		69	40	-	100	96
GLS mean ratio (%)[a]		80	104	-	94	90
90% Log-transformed CI[a]		69-93	84-129	-	87-102	82-99

The following table is a summary of PK parameters for Baseline-Adjusted Total Estrone (sponsor's table 8.10-1, section 8.10).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	2.75 ± 1.68	9.4 ± 4.4	17.7 ± 7.7	46.7 ± 26.3	50.9 ± 30.2
	CV, %	61.0	46.6	43.7	56.2	59.3
	Geometric mean	2.31	8.7	16.3	41.2	44.1
	Range	0.45-7.88	4.5-24.0	7.4-36.7	14.2-134.3	15.2-145.7
BZA 40 mg/CE 0.625 mg	Mean ± SD	2.06 ± 0.97	9.4 ± 2.4	18.3 ± 7.9	40.8 ± 17.8	43.5 ± 20.1
	CV, %	46.9	25.8	43.2	43.7	46.2
	Geometric mean	1.82	9.1	16.8	36.9	38.9
	Range	0.49-4.39	6.0-16.0	8.3-37.2	11.5-83.2	11.6-85.3
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.51	0.04	0.54	0.66	0.58
Treatment		0.02	0.74	0.94	0.13	0.13
Period		0.20	0.93	0.03	0.26	0.22
Statistical power		63	40	-	86	78
GLS mean ratio (%)[a]		79	104	-	90	88
90% Log-transformed CI[a]		67-93	84-129	-	80-101	77-101

The following table is a summary of PK parameters for Total Equilin (sponsor's table 8.11-1, section 8.11).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	1.83 ± 1.07	7.6 ± 2.7	11.5 ± 3.6	26.4 ± 18.5	28.4 ± 19.3
	CV, %	58.4	35.3	31.0	70.0	68.0
	Geometric mean	1.53	7.3	11.0	21.9	23.9
	Range	0.29-4.35	4.5-16.0	6.3-17.6	5.8-89.7	9.1-92.1
BZA 40 mg/CE 0.625 mg	Mean ± SD	1.48 ± 0.85	9.0 ± 2.8	12.1 ± 3.6	23.9 ± 14.4	25.3 ± 14.5
	CV, %	57.4	30.7	29.7	60.5	57.4
	Geometric mean	1.26	8.6	11.5	20.0	21.7
	Range	0.37-3.93	4.5-16.0	6.1-17.2	6.1-66.3	7.7-67.9
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.58	0.62	0.17	0.70	0.66
Treatment		0.02	0.20	0.35	0.20	0.16
Period		0.26	0.91	0.77	0.34	0.23
Statistical power		79	42	-	90	92
GLS mean ratio (%)[a]		82	117	-	92	91
90% Log-transformed CI[a]		72-94	95-145	-	82-103	82-102

The following table is a summary of PK parameters for Total 17β-Estradiol (sponsor's table 8.12-1, section 8.12).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	0.359 ± 0.189	10.2 ± 5.5	35.9 ± 20.3	6.31 ± 2.41	7.84 ± 3.63
	CV, %	52.5	54.2	56.6	38.2	46.3
	Geometric mean	0.319	9.2	31.9	5.90	7.15
	Range	0.127-0.921	4.5-24.0	14.0-102.1	2.99-12.68	3.41-15.59
BZA 40 mg/CE 0.625 mg	Mean ± SD	0.303 ± 0.127	9.9 ± 3.9	40.1 ± 16.4	5.93 ± 2.05	7.15 ± 2.47
	CV, %	41.9	39.0	40.8	34.6	34.6
	Geometric mean	0.274	9.4	37.2	5.58	6.74
	Range	0.097-0.511	6.0-24.0	19.6-76.9	2.79-10.66	3.63-12.77
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.07	0.15	0.05	0.17	0.06
Treatment		0.17	0.94	0.03	0.30	0.35
Period		0.74	0.23	0.76	0.59	0.54
Statistical power		53	58	-	97	90
GLS mean ratio (%)[a]		86	101	-	94	94
90% Log-transformed CI[a]		72-103	85-119	-	86-104	84-105

The following table is a summary of PK parameters for Baseline-Adjusted Total 17β-Estradiol (sponsor's table 8.13-1, section 8.13).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	0.347 ± 0.186	10.2 ± 5.5	17.1 ± 5.9	5.20 ± 1.98	5.72 ± 2.63
	CV, %	53.7	54.2	34.5	38.1	46.0
	Geometric mean	0.307	9.2	16.1	4.87	5.26
	Range	0.127-0.905	4.5-24.0	6.9-29.2	2.26-9.78	2.32-13.64
BZA 40 mg/CE 0.625 mg	Mean ± SD	0.291 ± 0.122	9.9 ± 3.9	17.8 ± 7.8	4.72 ± 1.41	5.01 ± 1.39
	CV, %	42.0	39.0	43.7	29.9	27.8
	Geometric mean	0.263	9.4	16.2	4.50	4.81
	Range	0.097-0.498	6.0-24.0	7.1-34.5	1.94-6.90	2.14-7.12
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.07	0.15	0.29	0.42	0.47
Treatment		0.17	0.94	0.99	0.23	0.22
Period		0.75	0.23	0.92	0.66	0.53
Statistical power		51	58	-	86	79
GLS mean ratio (%)[a]		86	101	-	92	91
90% Log-transformed CI[a]		72-103	85-119	-	81-104	80-104

Reference ID: 3319979

The following table is a summary of PK parameters for Total 17β-Dihydroequilin (sponsor's table 8.14-1, section 8.14).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	0.504 ± 0.296	9.2 ± 4.7	9.8 ± 4.0	7.34 ± 5.36	7.98 ± 5.60
	CV, %	58.7	50.8	40.9	73.0	70.2
	Geometric mean	0.422	8.4	9.0	6.04	6.68
	Range	0.083-1.130	4.5-24.0	3.5-19.3	1.92-24.78	2.60-25.58
BZA 40 mg/CE 0.625 mg	Mean ± SD	0.386 ± 0.183	9.1 ± 2.6	14.7 ± 14.1	6.24 ± 3.59	7.12 ± 3.59
	CV, %	47.3	28.6	96.6	57.4	50.5
	Geometric mean	0.343	8.8	11.9	5.32	6.41
	Range	0.115-0.865	4.5-16.0	6.3-69.3	1.45-16.48	2.37-18.35
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.41	0.47	0.42	0.49	0.31
Treatment		0.02	0.74	0.05	0.11	0.60
Period		0.15	0.71	0.41	0.26	0.20
Statistical power		73	30	-	84	76
GLS mean ratio (%)[a]		82	105	-	89	96
90% Log-transformed CI[a]		71-94	81-136	-	79-101	84-110

The following table is a summary of PK parameters for Total $\Delta^{8,9}$-Dehydroestrone (sponsor's table 8.15-1, section 8.15).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	0.499 ± 0.210	7.2 ± 1.3	44.0 ± 30.3	10.25 ± 4.11	13.71 ± 6.01
	CV, %	42.1	17.9	68.9	40.1	43.9
	Geometric mean	0.460	7.1	35.7	9.46	12.40
	Range	0.182-1.070	4.5-9.0	11.6-128.1	3.61-21.14	4.45-25.95
BZA 40 mg/CE 0.625 mg	Mean ± SD	0.436 ± 0.163	8.9 ± 2.0	47.5 ± 33.8	9.34 ± 3.40	12.33 ± 4.56
	CV, %	37.4	22.0	71.3	36.4	37.0
	Geometric mean	0.406	8.7	37.7	8.66	11.42
	Range	0.146-0.929	6.0-12.0	8.8-119.7	2.92-17.17	4.18-19.91
	p-Values From Log-Transformed Analysis of Variance					
Sequence		0.34	0.48	0.52	0.50	0.27
Treatment		0.02	0.001	0.47	0.14	0.29
Period		0.12	0.53	0.60	0.25	0.32
Statistical power		100	96	-	98	83
GLS mean ratio (%)[a]		89	124	-	92	92
90% Log-transformed CI[a]		82-96	113-137	-	84-101	82-105

Reference ID: 3319979

The following table is a summary of PK parameters for Total 17β-$\Delta^{8,9}$-Dehydroestradiol (sponsor's table 8.16-1, section 8.16).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
CE 0.625 mg	Mean ± SD	0.253 ± 0.111	8.9 ± 4.4	11.6 ± 5.0	3.86 ± 2.00	4.71 ± 2.29
	CV, %	43.7	49.9	43.5	51.8	48.5
	Geometric mean	0.225	8.2	10.6	3.40	4.30
	Range	0.048-0.442	4.5-24.0	3.7-22.5	0.78-8.69	2.18-10.73
BZA 40 mg/CE 0.625 mg	Mean ± SD	0.203 ± 0.073	9.3 ± 2.5	12.0 ± 4.0	3.21 ± 1.27	3.97 ± 1.26
	CV, %	36.0	26.4	33.1	39.6	31.8
	Geometric mean	0.187	9.0	11.5	2.90	3.78
	Range	0.048-0.340	6.0-16.0	6.6-23.1	0.64-5.88	1.86-7.22
	----------p-Values From Log-Transformed Analysis of Variance----------					
Sequence		0.41	0.28	0.77	0.68	0.52
Treatment		0.02	0.42	0.42	0.06	0.11
Period		0.19	0.45	0.61	0.37	0.38
Statistical power		80	44	.	79	82
GLS mean ratio (%)[a]		83	110	-	86	88
90% Log-transformed CI[a]		73-94	90-135	-	75-98	78-100

The following table is a summary of PK parameters for BZA (sponsor's table 8.17-1, section 8.17).

Treatment	Parameter	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
BZA 40 mg	Mean ± SD	7.65 ± 3.78	1.7 ± 2.0	22.8 ± 5.9	115.2 ± 48.7	123.9 ± 56.1
	CV, %	49.4	114.6	25.7	42.3	45.3
	Geometric mean	6.81	1.3	22.2	106.5	113.6
	Range	3.02-14.20	0.5-9.0	16.8-39.6	54.6-252.7	57.9-294.1
BZA 40 mg/CE 0.625 mg	Mean ± SD	9.03 ± 3.26	1.4 ± 1.2	24.0 ± 8.0	139.1 ± 59.8	151.4 ± 68.9
	CV, %	36.1	83.2	33.3	43.0	45.5
	Geometric mean	8.40	1.2	23.1	128.2	138.1
	Range	3.57-15.10	0.5-6.0	16.1-51.9	58.7-273.2	60.6-291.8
	----------p-Values From Log-Transformed Analysis of Variance----------					
Sequence		0.42	0.25	0.47	0.09	0.08
Treatment		0.06	0.18	0.21	0.006	0.006
Period		0.69	0.006	0.12	0.13	0.12
Statistical power		46	53	-	90	87
GLS mean ratio (%)[a]		126	87	-	123	124
90% Log-transformed CI[a]		103-153	72-104	-	110-138	110-140

<u>Safety Findings</u>

The following table summarizes the treatment-emergent adverse events following administration of a single dose of CE 0.625 mg alone, BZA 40 mg alone, or combination BZA 40mg/CE 0.625 mg (sponsor's table 9.2.1-1, section 9.2).

Body System Adverse event	CE 0.625 mg (n = 20)	BZA 40 mg (n = 20)	BZA 40 mg/ CE 0.625 mg (n = 21)	Total (n = 21)
Any adverse event	3 (15.0)	3 (15.0)	0	5 (23.8)
Body as a whole				
Back pain	0	1 (5.0)	0	1 (4.8)
Fever	0	1 (5.0)	0	1 (4.8)
Headache	1 (5.0)	2 (10.0)	0	3 (14.3)
Infection	0	1 (5.0)	0	1 (4.8)
Digestive system				
Constipation	1 (5.0)	0	0	1 (4.8)
Respiratory system				
Cough increased	1 (5.0)	0	0	1 (4.8)

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Reference ID: 3319979

Study 3115A1-1136-US

Title: "An Open-Label, Single-Dose, Randomized, 2-Period, Crossover, Relative Bioavailability Study of a Bazedoxifene/Conjugated Estrogens Tablet Compared with a Bazedoxifene Tablet in Healthy, Postmenopausal Women"

Objective: The primary objective of the study was to compare the BZA bioavailability from a combination BZA 20 mg/CE 0.45 mg tablet and a BZA 20 mg only tablet in healthy, postmenopausal women. The secondary objective was to obtain additional safety and tolerability data from both combination BZA/CE and BZA alone tablet.

Methods: This was a randomized, open-label, single-dose, 2-period, 2-treatment, crossover study in twenty-four healthy postmenopausal women. The mean (SD) age was 56 (7) yrs (range: 40 to 68 yrs) and mean (SD) weight was 67 (10) kg. Of the 24 subjects, 21 were White, 1 was Black, and 2 were American Indian. A single BZA 20 mg or BZA 20 mg/CE 0.45 mg tablet was administered with 240 mL of water following an overnight fast of at least 10 hrs and continued to fast until 4 hrs after drug administration. There was at least a 10-day washout period between each single dose administration.

This study was conducted at [redacted] (b) (4) from September 15 to 29, 2009.

Test Products

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA/CE (test)	20/0.45	Tablet	0932557C	D87931
BZA (reference)	20	Tablet	0931958C	C87519

Treatment A: BZA 20 mg /CE 0.45 mg tablet (test)
Treatment B: BZA 20 mg tablet (reference)

Pharmacokinetic Sampling: Blood samples for determination of BZA concentrations were taken 2 hrs predose, and 0.5, 0.75, 1, 1.5, 2, 3, 4.5, 6, 9, 12, 16, 24, 48, 72 and 96 hrs postdose in all treatment periods. Plasma samples were analyzed for BZA concentrations with LC/MS/MS method with a LLOQ of 40 pg/mL. The analyses were performed [redacted] (b) (4)

Results and Reviewer's Comments:
From this study it appears that only Cmax was affected. The Cmax of BZA was 49% higher for BZA/CE combination tablet (4.69 ng/mL), compared to BZA alone tablet (3.14 ng/mL). However, AUC of BZA was comparable when the tablet was administered alone (62.1 ng.hr/mL) or BZA/CE together 66.3 ng.hr/mL). Based upon AUC, there is minimal difference in BZA exposure between the combination and alone tablets. The following table summarizes the PK parameters of BZA following a single dose of BZA 20 mg and a single combination dose of BZA 20 mg/CE 0.45 mg (sponsor's table 8-1, section 8.1).

Mean ± SD	Treatment	
	BZA 20 mg	BZA 20 mg + CE 0.45 mg
N	24	24
C_{max}(ng/mL)	3.14 ± 1.25	4.69 ± 2.42
t_{max}[a] (hr)	1.00 (0.50 - 6.00)	1.00 (0.50 - 3.00)
$t_{1/2}$ (hr)	25.53 ± 8.08	24.61 ± 6.65
AUC_T (ng•hr/mL)	62.1 ± 30.1	66.3 ± 25.8
AUC (ng•hr/mL)	68.3 ± 33.4	72.6 ± 30.6

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The following table summarizes the statistical comparison of BZA following a single dose of BZA 20 mg and a single combination dose of BZA 20 mg/CE 0.45 mg (sponsor's table 8-2, section 8.1).

	p-Values from Log-Transformed Analysis of Variance		
	C_{max}	AUC_T	AUC
Factor	(ng/mL)	(ng•hr/mL)	(ng•hr/mL)
Period	0.0906	0.270	0.263
Sequence	0.0541	0.974	0.978
Treatment	0.00189	0.231	0.279
Intersubject CV%	24.6	34.3	37.0
Intrasubject CV%	34.5	27.3	26.9
	Pair-wise Comparison: BZA 20 mg + CE 0.45 mg (Test) vs. BZA 20 mg (Ref)		
Ratio of Least Square Geometric Means (%)	141	110	109
90% Confidence Interval around Ratio	119-166	96-126	95-124
Probability < 80%	0.00000362	0.000230	0.000278
Probability > 125%	0.883	0.0569	0.0417
Total Probability (<80%,>125%)	0.883	0.0571	0.0420
Statistical Power (%)	71.8	87.1	88.0

Study 3115A1-1138-US

Title: "An Open-Label, Multiple-Dose Study of Bazedoxifene/Conjugated Estrogens Tablets in Healthy Postmenopausal Women"

Objective: The primary objective of this study was to assess the steady-state PK profiles of BZA and CE using BZA/CE tablets. The secondary objective was to obtain additional safety and tolerability data of BZA/CE tablets in healthy postmenopausal women.

Methods: This was an open-label, multiple-dose study in twenty-four healthy postmenopausal women consisting of a 12-day, 11-night inpatient period and a follow-up phone call approximately 15 days after the last dose administered. The mean (SD) age was 56 (4) yrs (range: 50 to 64 yrs) and mean (SD) weight was 68 (9) kg.

Of the 24 subjects, 22 were White and 2 were Black. BZA 20 mg/CE 0.45 mg tablets were administered with 240 mL of room temperature water once daily for 10 days. On Days 1 and 10, tablets were given at approximately 8 am following an overnight fast of at least 10 hrs and water was permitted ad lib except from 2 hrs before until 2 hrs after drug administration. On Days 2 through 9, BZA/CE tablets were administered after breakfast.

The study was conducted by a single investigator (Audrey E. Martinez, MD), 3898 NW7th Street, Miami, FL from July 2009 to August 2009.

Test Product

Drug Product	Strength (mg)	Dosage Form	Formulation Number (Stock Number)	Batch Number
BZA/CE	20 mg/0.45 mg	Tablet	0932557C	D87931

Pharmacokinetics Sampling: Blood samples for determination of BZA and CE concentrations were taken at 0 (predose), 1.5, 3, 4.5, 6, 7.5, 9, 12, 16, and 24 hrs postdose on Days 1 and 10. Plasma samples were analyzed for BZA concentrations with LC/MS/MS method with a LLOQ of 40 pg/mL. Plasma samples were analyzed for estrone (an endogenous estrogen) and equilin by validated GC/MS/MS methods with a LLOQ for unconjugated estrone, unconjugated equilin, total estrone, and total equilin of 5, 10, 25, and 50 pg/mL, respectively. The analyses were performed (b) (4) PK parameters were reported for estrone (unconjugated estrone, baseline-corrected unconjugated estrone, total estrone, and baseline-corrected total estrone) and equilin (unconjugated equilin and total equilin); the two most abundant estrogens in CE.

Baseline Estrone: Baseline concentration of estrone for each subject was determined by taking plasma sample at 0 hr (predose) from Day 1. Plasma concentrations of estrone were adjusted for baseline by subtracting the baseline value. Concentrations less than zero after baseline adjustment were assumed to be zero. The same baseline concentration was used for Day 1 (single-dose) and Day 10 (multiple-doses) plasma concentration profile.

Results and Reviewer's Comments: Single- and multiple-dose PK of BZA and CE were assessed following once daily administration of BZA 20 mg/CE 0.45 mg tablets for 10 days in healthy postmenopausal women. BZA plasma concentrations were approximately double (R=2.06) after 10 days of daily administration compared to a single dose of BZA/CE. For all measures of estrone, mean accumulation ratios were around 2 (range: 1.54 to 2.36). For unconjugated equilin and total equilin, mean accumulation ratio was 4.1 and 1.4, respectively.

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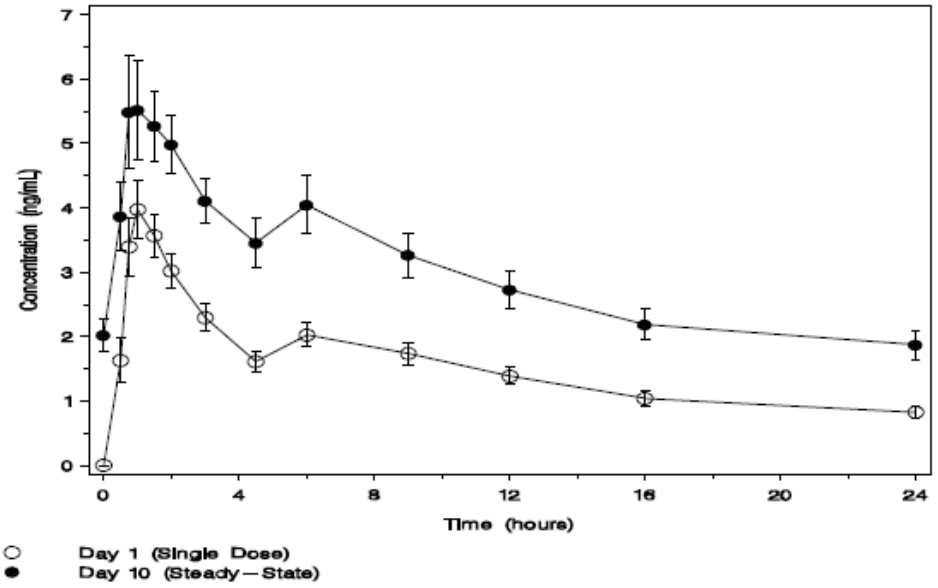
Previous PK studies (which studies with combination or mono tablet?) showed that BZA reaches steady-state in approximately 7 days and half-life is approximately 30 hrs. Because blood samples were not collected beyond 24 hrs, elimination rate and half-life of BZA were not estimated.

The multiple-dose data of BZA and CE following BZA/CE tablets show accumulation similar to previous studies of BZA and CE administered as separate tablets.

The following are the mean (SD) concentration-time profiles of BZA on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.33, section 14.0).

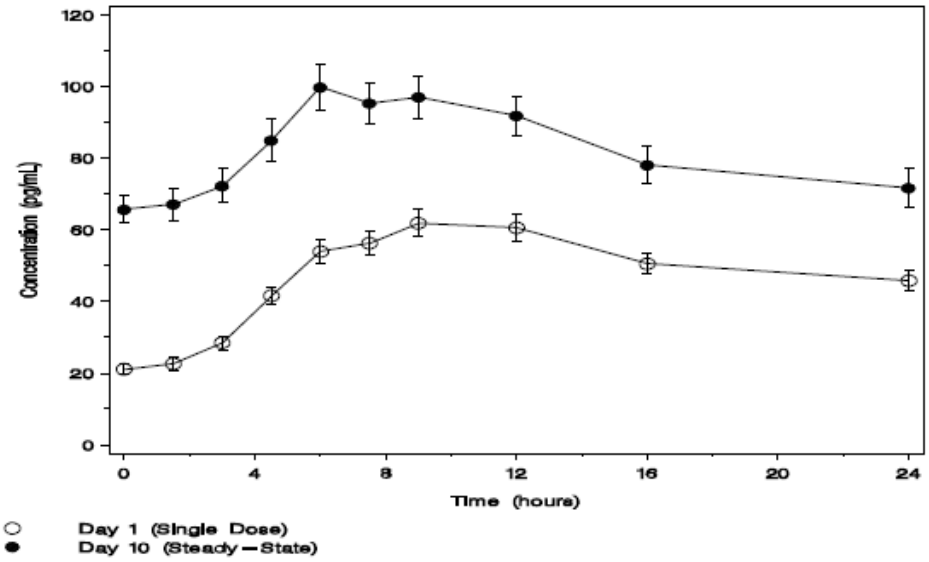


The following table summarizes the PK parameters of BZA on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-7, section 8.7).

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)

The following are the mean (SD) concentration-time profiles of Unconjugated Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.3, section 14.0).

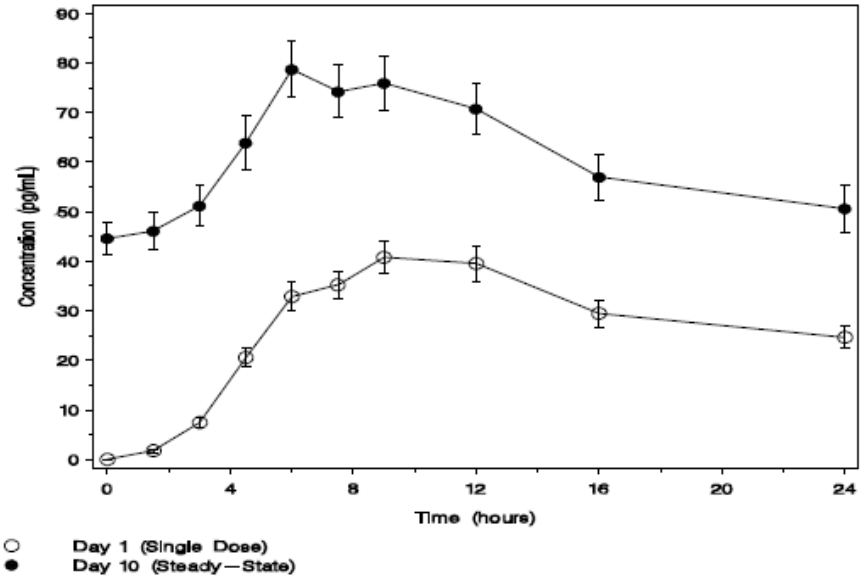
Reference ID: 3319979



The following table summarizes the PK parameters of Unconjugated Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-1, section 8.1).

Treatment		C_{max} (pg/mL)	t_{max} (h)	C_{min} (pg/mL)	AUC_{0-24h} (pg·h/mL)	R
Day 1	Mean ± SD	66.9 ± 19.5	10.4 ± 3.6		1156 ± 302	
(single-dose)	%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	Mean ± SD	110 ± 32.3	7.4 ± 4.3	61.6 ± 19.1	1970 ± 569	1.72 ± 0.36
(steady-state)	%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)

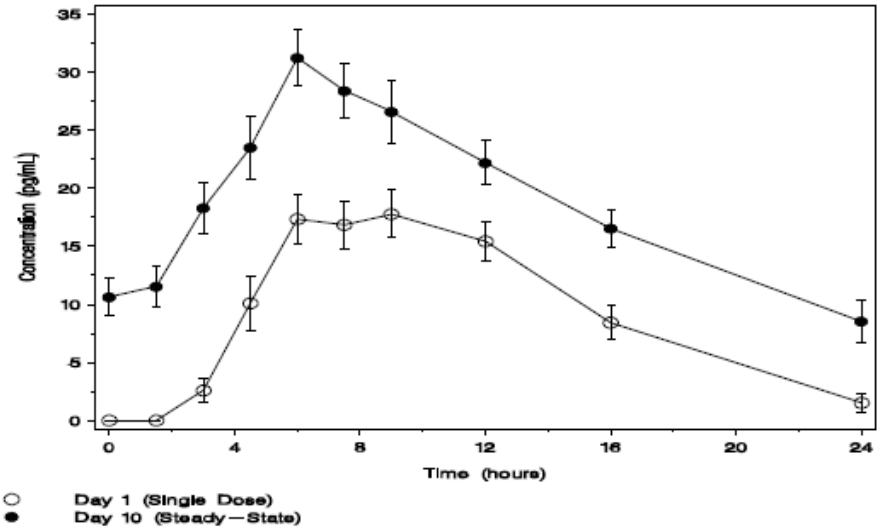
The following are the mean (SD) concentration-time profiles of Baseline-Adjusted Unconjugated Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.8, section 14.0).



The following table summarizes the PK parameters of Baseline-Adjusted Unconjugated Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-2, section 8.2).

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	45.8 ± 17.4	10.4 ± 3.6	-	649 ± 239	-
	%CV	38.1	34.9		36.8	
	N	24	24		24	
	Geometric Mean (Range)	43.0 (19.6-86.2)	9.9 (6.0-24.0)		610 (247-1293)	
Day 10 (steady-state)	Mean ± SD	88.7 ± 29.8	7.4 ± 4.3	40.5 ± 15.7	1463 ± 501	2.36 ± 0.85
	%CV	33.6	58.4	38.9	34.3	35.84
	N	24	24	24	24	24
	Geometric Mean (Range)	82.8 (22.7-144)	6.6 (1.5-24.0)	35.8 (2.9-70.1)	1351 (262-2359)	2.21 (0.64-4.76)

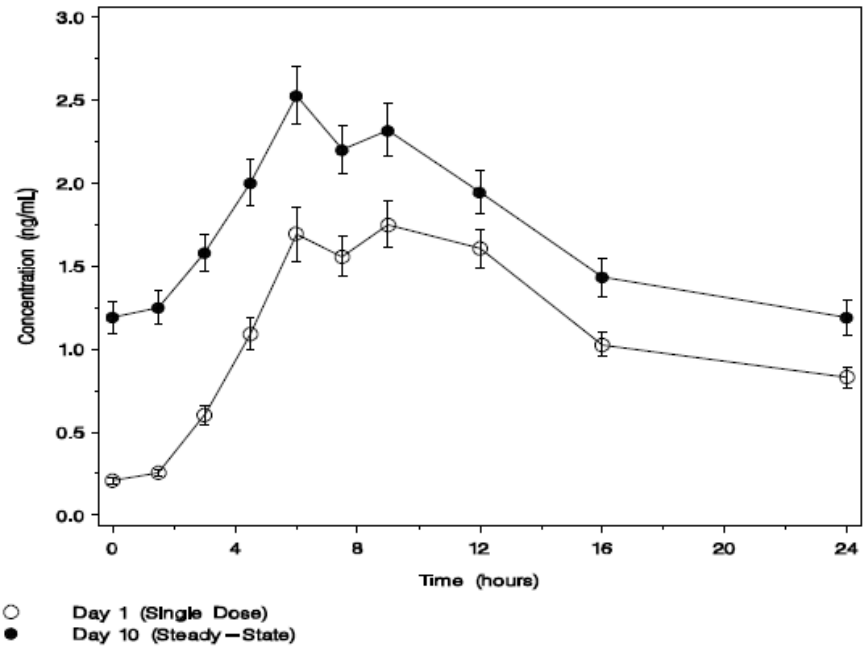
The following are the mean (SD) concentration-time profiles of Unconjugated Equilin on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.13, section 14.0).



The following table summarizes the PK parameters of Unconjugated Equilin on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-3, section 8.3).

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	21.8 ± 9.2	8.8 ± 4.4		193 ± 111	
	%CV	42.4	50.3		57.3	
	N	24	24		23	
	Geometric Mean	21.5	8.5		163	
	(Range)	(0.0-46.6)	(0.0-24.0)		(46-503)	
Day 10 (steady-state)	Mean ± SD	34.5 ± 11.7	6.5 ± 2.2	9.43 ± 6.66	587 ± 113	4.10 ± 3.79
	%CV	33.8	33.8	70.6	19.2	92.5
	N	24	24	24	13	13
	Geometric Mean	32.4	6.1	13.0	577	3.18
	(Range)	(12.9-55.9)	(1.5-12.0)	(0.0-19.8)	(414-821)	(1.63-13.7)

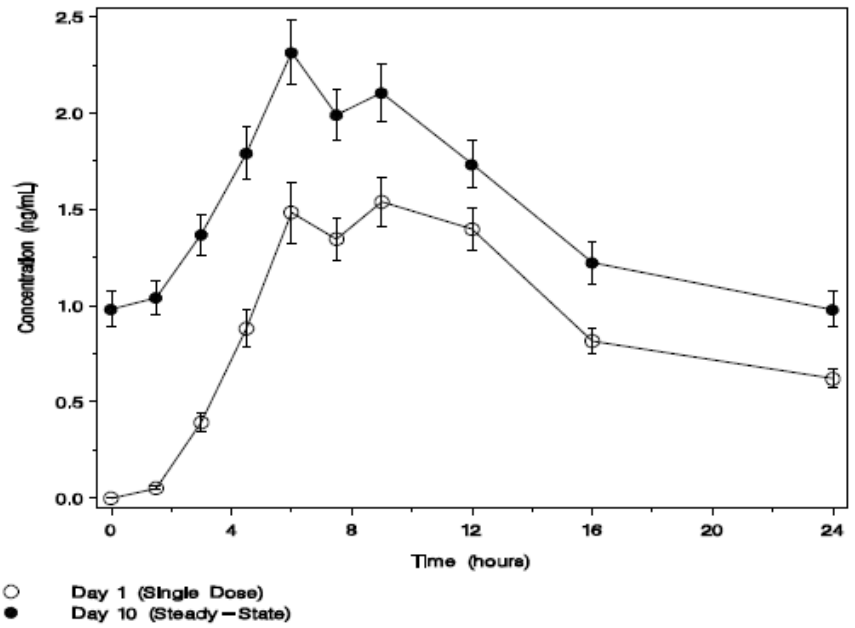
The following are the mean (SD) concentration-time profiles of Total Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.18, section 14.0).



The following table summarizes the PK parameters of Total Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-4, section 8.4).

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	2.05 ± 0.78	8.4 ± 2.6		26.8 ± 8.2	
	%CV	38.3	31.2		30.6	
	N	24	24		24	
	Geometric Mean	1.91	8.0		25.6	
	(Range)	(0.73-4.48)	(4.5-12.0)		(13.1-48.9)	
Day 10 (steady-state)	Mean ± SD	2.78 ± 0.81	6.5 ± 1.6	1.09 ± 0.46	40.4 ± 13.0	1.54 ± 0.41
	%CV	29.0	24.2	41.8	32.3	26.3
	N	24	24	24	24	24
	Geometric Mean	2.66	6.3	1.00	38.2	1.49
	(Range)	(1.01-4.46)	(4.5-9.0)	(0.30-1.98)	(14.2-68.1)	(0.83-2.67)

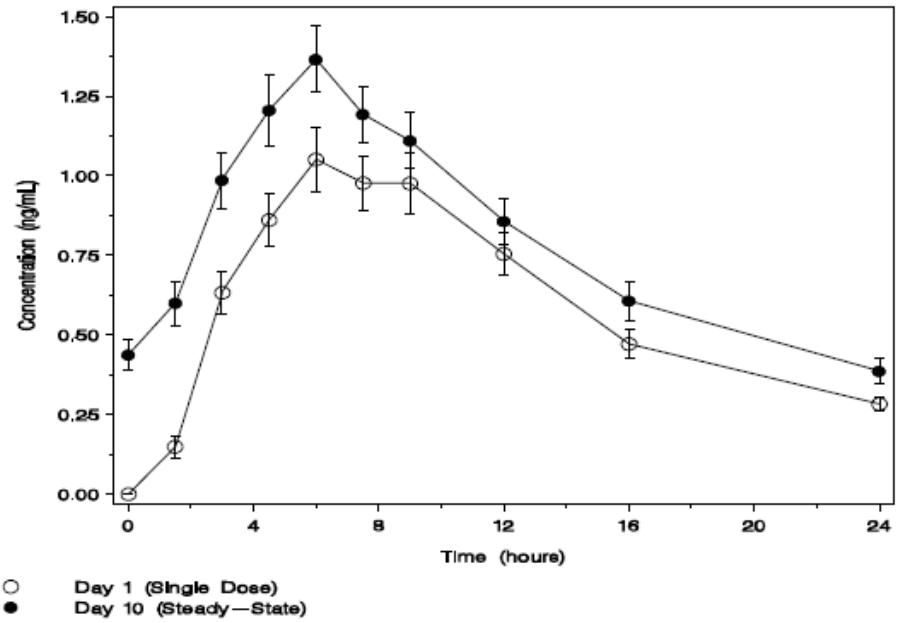
The following are the mean (SD) concentration-time profiles of Baseline-Adjusted Total Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.23, section 14.0).



The following table summarizes the PK parameters of Baseline-Adjusted Total Estrone on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-5, section 8.5).

Treatment		C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	R
Day 1 (single-dose)	Mean ± SD	1.84 ± 0.75	8.4 ± 2.6		21.7 ± 7.1	
	%CV	40.7	31.2		32.6	
	N	24	24		24	
	Geometric Mean	1.70	8.0		20.6	
	(Range)	(0.58-4.18)	(4.5-12.0)		(9.7-41.6)	
Day 10 (steady-state)	Mean ± SD	2.57 ± 0.76	6.5 ± 1.6	0.88 ± 0.41	35.4 ± 11.8	1.70 ± 0.56
	%CV	29.6	24.2	45.9	33.3	32.9
	N	24	24	24	24	24
	Geometric Mean	2.46	6.3	0.79	33.3	1.62
	(Range)	(0.94-4.13)	(4.5-9.0)	(0.23-1.77)	(12.5-63.0)	(0.79-3.45)

The following are the mean (SD) concentration-time profiles of Total Equilin on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's figure 14.28, section 14.0).



The following table summarizes the PK parameters of Total Equilin on Day 1 following a single dose of BZA 20 mg/CE 0.45 mg and on Day 10 following multiple doses of BZA 20 mg/CE 0.45 mg (sponsor's table 8-6, section 8.6).

Treatment		C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	R
Day 1 (single-dose)	Mean ± SD	1.27 ± 0.47	6.6 ± 2.1		14.1 ± 4.8	
	%CV	37.3	31.3		34.3	
	N	24	24		24	
	Geometric Mean	1.19	6.3		13.2	
	(Range)	(0.50-2.76)	(3.0-12.0)		(5.0-24.5)	
Day 10 (steady-state)	Mean ± SD	1.55 ± 0.48	5.4 ± 1.6	0.36 ± 0.19	18.9 ± 7.0	1.40 ± 0.48
	%CV	30.9	30.2	52.7	37.3	34.6
	N	24	24	24	24	24
	Geometric Mean	1.48	5.2	0.31	17.6	1.33
	(Range)	(0.77-2.86)	(3.0-9.0)	(0.06-0.93)	(5.8-38.6)	(0.52-3.01)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAYED AL HABET
06/05/2013

LAI M LEE
06/05/2013

FANG LI
06/05/2013

YANING WANG
06/05/2013
Signing for the Pharmacometrics component.

MYONG JIN KIM
06/05/2013

EDWARD D BASHAW
06/05/2013
This document consists of the Individual Study Reports for the primary clin pharm review of NDA 022247

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 22-247	**Reviewers:** Kareen Riviere, Ph.D. John Z. Duan, Ph.D.	
Submission Dates:	10/3/2012; 2/19/2013; 4/12/2013; 4/15/13; 5/17/2013		
Division:	DRUP	**Acting Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Wyeth	**Biopharmaceutics Supervisor (acting):** Richard Lostritto, Ph.D.	
Trade Name:	(b) (4)	**Date Assigned:**	11/2/2012
Generic Name:	Bazedoxifene/ Conjugated Estrogens	**Date of Review:**	5/29/2013
Indication:	Treatment of moderate to severe vasomotor symptoms due to menopause; treatment of moderate to severe vulvar and vaginal atrophy; prevention of post-menopausal osteoporosis.	**Type of Submission:** 505(b)(1) Original NDA	
Formulation/Strengths:	Tablet; BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(1) New Drug Application for Bazedoxifene/Conjugated Estrogens (BZA/CE) tablets. The proposed to be marketed tablet strengths are 20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE. The proposed indications are for the treatment of moderate to severe vasomotor symptoms, treatment of moderate to severe vulvar and vaginal atrophy, and prevention of postmenopausal osteoporosis.

Bazedoxifene/Conjugated Estrogens (BZA/CE) tablets are a fixed dose combination produc (b) (4)

This submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criteria for BZA and CE, an *in vitro in vivo* correlation (IVIVC) for BZA/CE tablets, and an *in vitro in vivo relationship* (IVIVR) (b) (4)

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed dissolution acceptance criteria for BZA and CE, 3) the IVIVC for the BZA/CE tablets, and 4) the IVIVR (b) (4)

A. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	50 rpm	900 mL	37°C	Water with 0.1% SLS

The proposed dissolution method has adequate discriminating power, and therefore is deemed acceptable.

Reference ID: 3316035

B. Dissolution Acceptance Criteria
The proposed dissolution acceptance criteria are shown below.

Acceptance Criteria for BZA
NMT (b) (4) at 15 minutes
(b) (4) (b) (4)
NLT (b) (4) at 60 minutes

Acceptance Criteria for CE
(b) (4) at 2 hours
(b) (4) at 3 hours
NLT (b) (4) at 8 hours

The proposed dissolution acceptance criteria for CE are deemed acceptable. The proposed dissolution acceptance criteria for BZA are considered (b) (4) In an IR letter to the Applicant dated March 28, 2013, the ONDQA Biopharmaceutics Team recommended dissolution acceptance criteria of **NMT** (b) (4) **release at 15 minutes** and **NLT** (b) (4) **release at 60 minutes** based on the mean *in vitro* dissolution profiles of the pivotal clinical and primary stability batches for both strengths. In a submission dated May 17, 2013, the Applicant proposed dissolution acceptance criteria of **NMT** (b) (4) **release at 15 minutes** and **NLT** (b) (4) **release at 60 minutes.** The ONDQA Biopharmaceutics Team deems the Applicant's final proposal acceptable. The agreed dissolution acceptance criteria are shown below.

Acceptance Criteria for BZA
NMT (b) (4) at 15 minutes
NLT (b) (4) at 60 minutes

Acceptance Criteria for CE
(b) (4) at 2 hours
(b) (4) at 3 hours
NLT (b) (4) at 8 hours

C. *In Vitro* Alcohol Interaction Study
Based on the provided *in vitro* data, there appears to be no *in vivo* alcohol dose-dumping potential for CE.

D. *In Vitro In Vivo Relationship* (IVIVR) for BZA Performance
The Applicant provided adequate data demonstrating that there is an IVIVR (b) (4)

E. *In Vitro In Vivo* Correlation (IVIVC) for BZA/CE Tablets
The proposed IVIVC for BZA/CE tablets is not deemed acceptable for the following reasons:
(b) (4)

RECOMMENDATIONS:

1. BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg tablets are recommended for approval from a Biopharmaceutics standpoint.
    - The following dissolution method and acceptance criteria for the tablets are recommended and have been agreed upon with the Applicant (submission dated May 17, 2013):

i. Dissolution Method:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	50 rpm	900 mL	37°C	Water with 0.1% SLS

ii. Dissolution Acceptance Criteria:

Acceptance Criteria for BZA
NMT (b) (4) at 15 minutes NLT (b) (4) at 60 minutes

Acceptance Criteria for CE
(b) (4) at 2 hours (b) (4) at 3 hours NLT (b) (4) at 8 hours

2. The proposed IVIVC for BZA/CE tablets is not recommended for approval. The following comments should be conveyed to the Applicant:

Your proposed IVIVC cannot be approved at this time due to the following reasons.

(b) (4)

In addition, the following concerns should be noted:

(b) (4)

(b) (4)

This information is valuable and can be used for further development of this product. If you want to pursue further the IVIVC model, conduct the following:

1) Build an IVIVC model using BZA-CE tablet data and validate the model.
2) Show the robustness of the model.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Duan, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

Bazedoxifene (BZA)

BZA is classified as a BCS class 2 (low solubility/high permeability) compound. The structure of bazedoxifene acetate is shown in Figure 1.

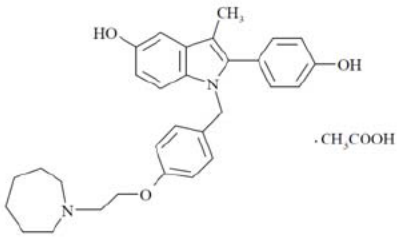


Figure 1. Chemical structure of bazedoxifene acetate

The Applicant conducted polymorphic screening on the BZA drug substance (b) (4)

(b) (4)

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2. Dissolution Method (reviewed by Dr. Kareen Riviere)

The proposed dissolution method for the BZA/CE tablets is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	50 rpm	900 mL	37°C	Water with 0.1% SLS

(b) (4)

CE Dissolution

(b) (4)

Figure 8 displays CE dissolution profiles for slow, medium, and fast release PREMARIN® batches using the approved dissolution method for PREMARIN® and the proposed dissolution method for BZA/CE tablets.

Reviewer's Assessment:

Figure 7 demonstrates that the proposed dissolution method provides a gradual release of CE over 8 hours.The release rate of PREMARIN® is similar to that of CE in BZA/CE tablets when tested using their respective dissolution methods. The data in Figure 8 demonstrate that the proposed dissolution method can discriminate different formulations of PREMARIN®. However, (b) (4)

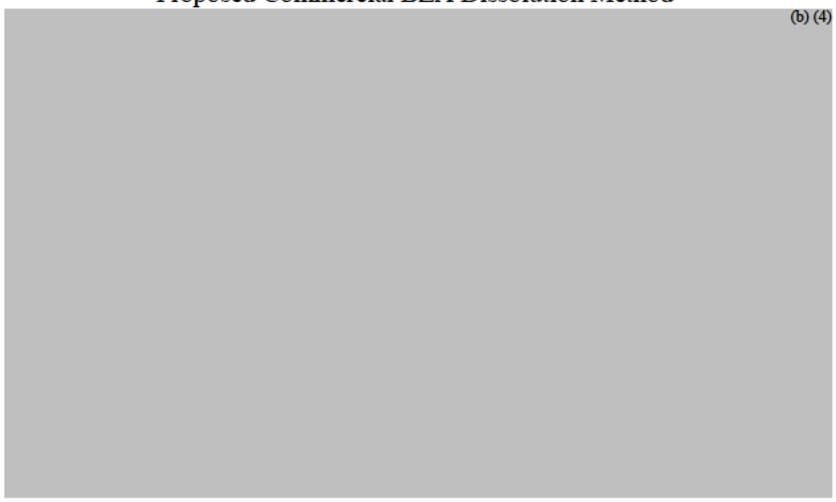
BZA Dissolution

Reviewer's Assessment:
The Applicant did not provide any justification for their selection of the dissoluttion medium, paddle speed, surfactant type, or surfactant concentration. However, the data in Figure 9 demonstrate that the proposed dissolution method can discriminate formulation changes. Also, there is an in vitro rank order to the in vivo profiles (refer to Figures 9 and 10).

Evaluating the Discriminating Ability of the Dissolution Method

BE vs. Non-BE Batches
Figure 11 depicts the dissolution profiles of batches (using the proposed commercial BZA dissolution method) that the Applicant determined were BE and non-BE to pivotal clinical formulation A.

Figure 11. Discrimination of Bioequivalent and Non-Bioequivalent Batches by the Proposed Commercial BZA Dissolution Method



Reviewer's Assessment:
The proposed dissolution method can discriminate BE from non-BE batches. Note that the dissolution method is a bit over-discriminating since batch C81416 is not f2 similar to batches D84412 and D71144 even though these batches are bioequivalent.

Effect of Particle Size on BZA Dissolution
The Applicant investigated the effect of API particle size on BZA dissolution (b) (4) They carried out two separate studies covering a range of API particle size distributions as shown in Table 5.

Table 5. BZA Particle Size Data (b) (4)

(b) (4)

Figures 12 and 13 show the dissolution profiles of BZA/CE tablet lots manufactured with particles size distrubitions listed in Table 5.

Figure 12. Effect of API Particle Size (D50) on the Dissolution of BZA from Tablets (b) (4) – Study #1

(b) (4)

Figure 13. Effect of API Particle Size (D50) on the Dissolution of BZA from Tablets (b) (4) – Study #2

(b) (4)

Reviewer's Assessment:
Figures 12 and 13 demonstrate (b) (4) ***from the BZA/CE tablets, as expected.***
(b) (4)

(b) (4)

Effect (b) (4) on Dissolution and Bioavailability

(b) (4)

Reviewer's Assessment:

(b) (4)

Overall, the proposed dissolution method has acceptable discriminating ability for both CE and BZA; therefore, it is an acceptable quality control method for CE and BZA.

3. Dissolution Acceptance Criteria (reviewed by Dr. Kareen Riviere)

The proposed dissolution acceptance criteria are shown below.

Acceptance Criteria for BZA
NMT (b) (4) at 15 minutes
(b) (4) at 40 minutes
NLT (b) (4) at 60 minutes

Acceptance Criteria for CE
(b) (4) at 2 hours
(b) (4) at 3 hours
NLT (b) (4) at 8 hours

CE Dissolution Acceptance Criteria

The Applicant based the proposed dissolution acceptance criteria for CE on clinical batch D85525 (BZA 20 mg/CE 0.45 mg). This batch was administered in the pivotal bioequivalence studies 3115A1-1137-US and 3115A1-1142-US. The Applicant stated that the average profile for this batch was obtained using the initial batch release results (n=12 tablets) and the initial stability results for the tablets in the two packaging systems (n=12 tablets each) provided in Table 7.

Table 7. CE Dissolution Data used to Justify Dissolution Acceptance Criteria for CE in the BZA/CE Tablets

Method: STM-00003181 (Formerly L27576-087) Acceptance Criteria: (b) (4)				
Batch # (Strength)	**Batch Use**	**Time Point (hours)**	**Individual Tablet Results (%Released)**	**Mean (Range) (%Released)**
D85525 [a, b] (20 mg/0.45mg) Release Results	Stability/ Clincial	2	(b) (4)	31 (b) (4)
		3		50
		8		96 (
D85525 Initial Stability Results (Bottles)		2		30
		3		48
		8		93
D85525 Initial Stability Results (Blisters)		2		29
		3		48
		8		92
Overall Mean and Range (N=36 Tablets)				
2 hours				30
3 hours				49
8 hours				94 (

a. Registration stability batch.
b. IVIVC biobatch (RPT 79146).

Reference ID: 3316035

Reviewer's Assessment:

(b) (4)

Thus, the proposed dissolution acceptance criteria for CE are acceptable.

BZA Dissolution Acceptance Criteria

Figure 15 shows the BZA dissolution profiles of the four tablet batches that were bioequivalent to Formulation A (i.e., D71144, D85525, D84442, and C81416), the two batches that were found to be non-bioequivalent to Formulation A (i.e., C88092 and C43766), and the five registration stability batches for the two tablet strengths.

Figure 15. BZA Dissolution Profiles of Batches Used to Set BZA Dissolution Acceptance Criteria

(b) (4)

Table 8 summarizes the mean and range of the dissolution data for the batches depicted in Figure 15.

Table 8. BZA Dissolution Data for Batches Used to Set BZA Dissolution Acceptance Criteria

Method: STM-00006683 (Formerly L42857-048) Acceptance Criteria: (b) (4)				
Batch # (Strength)	**Batch Use**	**Time Point (min)**	**Individual Tablet Results (%Released)**	**Mean (Range) (%Released)**
D85525 [a] (20 mg/0.45mg)	Stability/ Clincial	15	(b) (4)	29 (b) (4)
		40		90
		60		97
D95217 [a] (20 mg/0.45mg)	Stability	15		38
		40		90
		60		98
D44163 [a] (20 mg/0.45mg)	Stability	15		32
		40		90
		60		97
D71144 (20 mg/0.45mg)	Stability/ Clincial	15		26
		40		88
		60		95
D84442 (20 mg/0.45mg)	Stability/ Clincial	15		30
		40		90
		60		97
C81416 (20 mg/0.625mg)	Clinical	15		17
		40		78
		60		90
C88092 (20 mg/0.625mg)	Clinical	15		10
		40		50
		60		67
C43766 (20 mg/0.625mg)	Clinical	15		10
		40		57
		60		75
F25949 [a] (20 mg/0.625mg)	Stability	15		39
		40		91
		60		96
F25950 [a] (20 mg/0.625mg)	Stability	15		42
		40		93
		60		98
F25952 [a] (20 mg/0.625mg)	Stability	15		37
		40		93
		60		98

a. Registration stability batch

Reviewer's Assessment:

The data in Figure 15 demonstrate that the proposed dissolution acceptance criteria can discriminate non-BE batches. However, the data in Table 8 indicate (b) (4) ***at each time-point. Therefore the following IR comment was conveyed to the Applicant on March 28, 2013.***

FDA Comment

1. The following dissolution acceptance criteria are recommended for BZA:
   NMT (b) (4) at 15 minutes
   (b) (4) at 40 minutes

NLT (b) (4) at 60 minutes

This recommendation is based on the mean *in vitro* dissolution profiles of the pivotal clinical and primary stability batches (24 months) for both strengths. Note that the setting of dissolution acceptance criteria is based on mean data (n=12 units) not on individual data; therefore, some batches may require Stage 2 and, occasionally, Stage 3 testing. Revise the acceptance criteria for the dissolution test accordingly and submit the updated table of specifications for the drug product.

Based on the Applicant's response submitted on April 12, 2013, the following comments were conveyed in an IR letter dated May 10, 2013.

FDA Comment

1. The following dissolution acceptance criteria are recommended for BZA:

NMT (b) (4) at 15 minutes

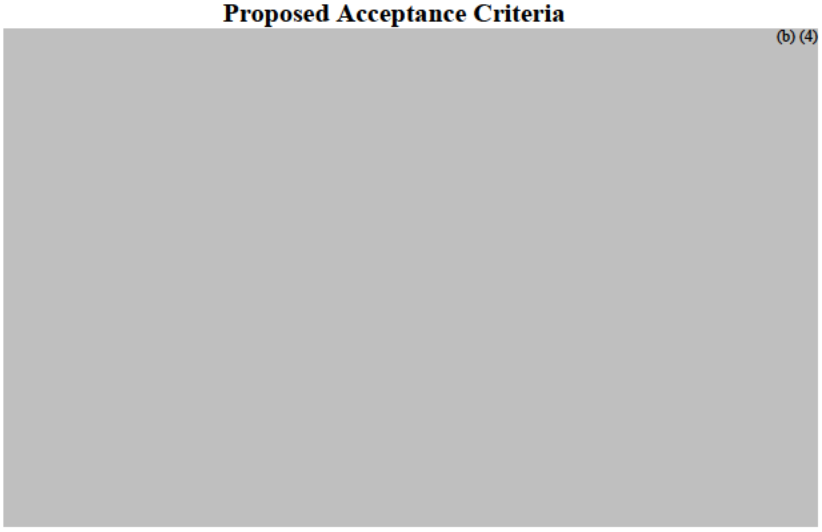
NLT (b) (4) at 60 minutes

This recommendation is based on the mean *in vitro* dissolution profiles of the pivotal clinical and primary stability batches for both strengths. Note that the setting of dissolution acceptance criteria is based on mean data (n=12 units) not on individual data; therefore, some batches may require Stage 2 and, occasionally, Stage 3 testing. Revise the acceptance criteria for the dissolution test accordingly and submit the updated table of specifications for the drug product.

Applicant's Response (excerpt)

Wyeth accepts the Agency's recommended acceptance criterion of NLT (b) (4) at 60 minutes for BZA dissolution. As shown, this acceptance criterion discriminates between bioequivalent and non-bioequivalent batches.

Mean BZA Dissolution Results for Key Samples Compared to Proposed Acceptance Criteria



Wyeth proposes (b) (4) the acceptance criterion at 15 minutes for BZA dissolution from the originally proposed value of NMT (b) (4) to NMT (b) (4) As shown, the BZA dissolution results for bioequivalent batches and registration stability batches of BZA/CE tablets would meet Wyeth's proposed acceptance criterion of NMT (b) (4) at 15 minutes. For example, the release results for 12 tablets from registration stability batch F25950 would meet Wyeth's proposed acceptance criterion at the Level 2 stage of testing.

However, this is not the case with Agency's proposed specification of NMT (b) (4) at 15 minutes. As discussed in the previous IR response submitted 12 April 2013, the mean release result at 15 minutes was (b) (4) for registration stability batch F25950. Therefore, this batch does not meet the Agency's proposed acceptance criterion at the Level 2 stage of testing.

Furthermore, Wyeth has subsequently employed statistical simulations as described in our previous response to determine that there is a 98% probability that registration stability batch F25950 would fail to meet the Agency's proposed acceptance criterion at Level 3 testing and therefore be rejected. Wyeth believes that it is unreasonable to reject a registration stability batch that would be expected to be bioequivalent to the pivotal clinical formulations.

Reviewer's Assessment:
The Applicant's justification is reasonable; therefore, their final proposed dissolution acceptance criteria as described below for BZA are acceptable.

Acceptance Criteria for BZA
NMT (b) (4) at 15 minutes
NLT (b) (4) at 60 minutes

4. In Vitro Alcohol Interaction Study (reviewed by Dr. Kareen Riviere)

The Applicant did not investigate the affect of alcohol (b) (4). Therefore, the following Biopharmaceutics IR comment was conveyed to the Applicant on February 1, 2013.

FDA Comment

1) We are concerned that your product may release its entire contents ("dose dumping") when used with alcohol, thereby leading to safety concerns. Therefore, we recommend that you conduct a drug-alcohol interaction study with your product. You should conduct *in vitro* drug release testing first using the highest strength according to the following guidelines:
   a. The following alcohol concentrations for the *in vitro* dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
   b. Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. Since the optimal dissolution medium has not been identified for your product, dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
   c. Report f2 values to assess the similarity (or lack thereof) in the dissolution profiles.
      - Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.
          - The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

Applicant's Response (excerpt)

(b) (4) Wyeth has conducted in vitro dissolution tests in ethanolic media to assess the potential for in vivo alcohol-induced dose dumping of CE from BZA/CE tablets. As requested, the dissolution media were prepared by adding differing amounts of ethanol to 0.1 N HCl and the proposed commercial dissolution medium for BZA/CE tablets (i.e., 0.1% sodium lauryl sulfate or SLS) to obtain solutions containing approximately 0%, 5%, 20%, and 40% alcohol.

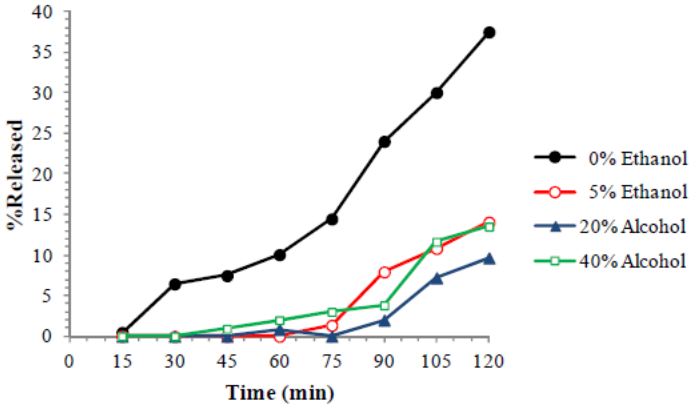
Twelve tablets of the highest dosage strength of this drug product (i.e., BZA 20 mg/CE 0.625 mg tablets) were tested using USP Apparatus 2 with paddles rotating at 50 rpm (as specified in STM-00003181, the proposed commercial CE dissolution method for BZA/CE tablets) in 900 mL of the ethanolic solutions at 37 ± 0.5°C. Dissolution samples were collected every 15 minutes for a total of 2 hours and analyzed using gradient reversed-phase HPLC as directed in STM-00003181.

The *f*2-test was not applied to the data collected during this study as the mean CE dissolution results for the BZA/CE tablets tested in the dissolution media with 0%, 5%, 20%, or 40% ethanol

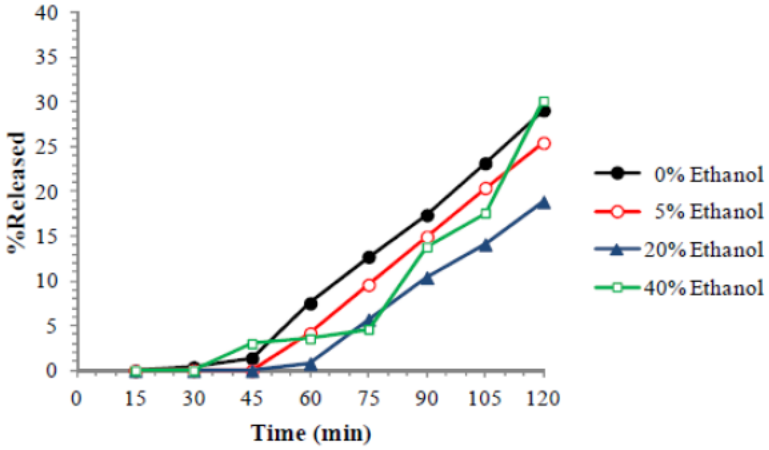
Reference ID: 3316035

are comparable or lower in 0.1 N HCl without ethanol or 0.1% SLS without ethanol, as shown in Figure 1 and Figure 2. Therefore, these studies clearly demonstrate that CE dose dumping does not occur when BZA/CE tablets are exposed to ethanolic media prepared using 0.1 N HCl or the proposed dissolution medium of 0.1% SLS.

Mean Drug Release Profiles for CE from BZA/CE tablets in Alcoholic Media Prepared by Adding Ethanol to 0.1 N HCl



Mean Drug Release Profiles for CE from BZA/CE tablets in Alcoholic Media Prepared by to the Proposed Dissolution Medium of 0.1% SLS



Reviewer's Assessment:

The data demonstrate that the presence of alcohol does not increase the in vitro release rate of CE. Thus, the Applicant provided adequate data demonstrating that there is no in vitro alcohol dose-dumping of CE. However, the data show that the presence of alcohol decreases the in vitro release rate of CE.

5. Evaluation of IVIVR (b) (4)
(reviewed by Dr. Kareen Riviere)

(b) (4)

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Reference ID: 3316035

(b) (4)

7. The IVIVC Study (reviewed by Dr. John Duan)

***In Vitro* Studies**

(b) (4)

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Reference ID: 3316035

Comments

The following comments should be conveyed to the Applicant:

Your proposed IVIVC cannot be approved at this time due to the following reasons.

In addition, the following concerns should be noted:

Reference ID: 3316035

(b) (4)

(b) (4)

This information is valuable and can be used for further development of this product.

If you want to pursue further the IVIVC model, conduct the following:

1) *Build an IVIVC model suing BZA-CE tablet data and validate the model.*
2) *Show the robustness of the model.*

Reference ID: 3316035

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAREEN RIVIERE
05/29/2013

JOHN Z DUAN
05/29/2013

TAPASH K GHOSH
05/29/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

FINAL
(December 5, 2012)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	022247	Brand Name	TBD™
OCP Division (I, II, III, IV, V)	III	Generic Name	Bazedoxifene **(BZA)**/ Conjugated estrogens (**CE, Premarin®**)
Medical Division	DRUP	Drug Class	Selective estrogen receptor modulator (SERM) and estrogen receptor agonist
OCP Reviewer	Sayed (Sam,) Al Habet, R.Ph., Ph.D.	Indication (s)	Three indications: Treatment of moderate to severe Vasomotor Symptoms (VMS), moderate to severe symptoms of vulvar and vaginal atrophy (VVA), and prevention of postmenopausal osteoporosis
OCP Secondary Reviewer/Signer	Myong-Jin Kim, Pharm.D.	Dosage Form	20mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Pharmacometrics Reviewer	Fang Li, Ph.D.	Proposed Dosing Regimen	20mg/0.45mg or 20mg/0.625mg daily
Date of Submission	September 26, 2012 (cover letter) October 3, 2012 (Receipt date)	Route of Administration	Oral
Estimated Due Date of OCP Review	May 2013	Sponsor	Wyeth/Pfizer
Medical Division Due Date	June 2013	Priority Classification	Standard
PDUFA Due Date	October 3, 2013 (***PDUFA 5 Goal Dated***)		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology	x	40		
Mass balance:		1		
Isozyme characterization:		1		
Blood/plasma ratio:				
Plasma protein binding:		1		
Pharmacokinetics (e.g., Phase I) -	x	40		
Healthy Volunteers-				
single dose:	x	25		
multiple dose:	x	3		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

Deleted:

fasting / non-fasting single dose:		2		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies		**7**		
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:		1		
renal impairment:				
hepatic impairment:		1		
PD -				
Phase 2:	x			
Phase 3:	x	3		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	2		
Population Analyses -		4		
Data rich:	x	4		
Data sparse:	x	4		
II. Biopharmaceutics		15		
Absolute bioavailability	x	1		
Relative bioavailability -	x	15		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -		15		
traditional design; single / multi dose:	x			
replicate design; single / multi dose:	x			
Food-drug interaction studies	x	2		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	x			
***In vitro* Penetration Studies**				

Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies		40		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	

16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes_

Executive Filing Summary:

What is the rationale for this Combination Product?

This is a combination of a New Molecular Entity (NME), Bazedoxifene (BZA also known as TSE-424) which is a third generation selective estrogen receptor modulator (SERM) and estrogen receptor agonist, conjugated estrogens (Premarin®). Mechanistically, the combination product is referred to as tissue-selective estrogen complex (TSEC).

BZA and CE function by binding to and activating the two estrogen receptors (α and β). CE is composed of multiple estrogens that demonstrate tissue selective estrogen receptor agonist activity. Bazedoxifene demonstrates both tissue selective estrogen receptor agonist and antagonist activity, exhibiting agonist activity on the skeletal system, while acting as an estrogen antagonist in breast and uterine tissue.

The rationale for the development of BZA/CE is based on the hypothesis that BZA will be acting primarily as an estrogen receptor antagonist in uterine and breast tissue. This will inhibit the proliferative effects of CE on the endometrium and reduce the incidence of uterine bleeding, breast pain/tenderness, and increased breast density associated with existing traditional progestin-containing hormone therapy (HT). CE is expected to effectively relieve menopause related symptoms (e.g., hot flushes, symptoms of VVA, vaginal dryness, and dyspareunia). In addition, in view of the positive effects of CE and BZA on the skeleton, it is expected that the combination of the 2 agents would be effective in the prevention of postmenopausal osteoporosis.

Historical Perspective of BZA:

BZA is approved in Europe, Japan and other countries for the treatment of postmenopausal osteoporosis. (b) (4)

Formulation and Formulation Development:

BZA/CE tablets are a fixed dose combination produc (b) (4) The proposed to-be-marketed (TBM) tablet strengths are 20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE.

BZA acetate drug substance is the same as that used in the BZA monotherapy product (b) (4)

The proposed TBM formulations consist of the commercial 0.45 mg or 0.625 mg Premarin® (b) (4)

The sponsor conducted extensive formulation and process development, dissolution development, and **15** biopharmaceutics (bioavailability and bioequivalence) studies including effect of food studies for the development the final proposed TBM BZA/CE drug product (**Appendix 1**). Studies for both the BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg dose strengths are described herein. Furthermore, the sponsor performed in-vitro-in-vivo (IVIVC) analysis.

In addition, the sponsor conducted additional **25** clinical pharmacology studies to characterize the PK of BZA and CE following BZA alone and in combination with CE (**Appendix 2**).

Summary of Formulation Development Studies:

As stated above, 15 bioavailability /bioequivalent studies were conducted to establish the link among several formulations used in Phase I, II and III studies. The following is the definition of important terms used in these studies:

- Premarin current process (**PCP**) formulation: Refers to the formulation used to manufacture Premarin tablets for the US market prior to 2004, which utilized a (b) (4) . **Formulation A** utilizes a PCP (b) (4)
- Premarin new process (**PNP**) formulations**:** refers to the formulation used to manufacture Premarin tablets for the US market after 2004, which utilizes (b) (4) . **Formulations B, C, and D** (including the proposed TBM formulations) utilize a PNP (b) (4)

- **Formulation A:** With a PCP CE (b) (4) that share a similar composition, but differ in the strength of BZA and CE.

- **Formulation B:** With PNP CE (b) (4) and share a similar composition, but differ in the strength of BZA and CE.

- **Formulation C:** (b) (4) change in Formulation B tablets

- **Formulation D: F**ormulations that share a similar composition but differ in (b) (4) . Formulation D was only used in Phase 1 clinical studies.

Table 1 lists and summarizes the formulations used in relevant studies submitted in this NDA's:

Table 1. Formulations Used in Clinical Pharmacology and Clinical Studies

Formulation	A	B	C	D (Including Proposed TBM)
Type of Study	2-year Phase 3 endometrial safety, BMD, VVA, and VMS study (3115A1-303-US/EU/BR) 1-year Phase 3 endometrial safety and osteoporosis prevention study (3115A1-3307-WW) Food Effect study (3115A1-102-US) Drug Interaction Study (3115A1-101-US) BA/BE Studies (3115A1-100-US, 3115A1-109-US, 3115A1-114-US, 3115A1-1120-US, 3115A1-1121-US, 3115A1-1117-US, 3115A1-1122-US, 3115A1-1137-US, 3115A1-1117-US	2-year Phase 3 endometrial safety and BMD study (3115A1-304-WW) 3-month Phase 3 VMS study (3115A1-305–US) 3-month Phase 3 VVA study (3115A1-306-WW) BA/BE Studies (3115A1-1117-US, 3115A1-1139-US, 3115A1-1142-US IVIVC Study (3115A1-115-US)	Phase 3 Study 3115A1-304-WW Used Formulation C for 8 months of first year and all of second year BA/BE Studies (3115A1-114-US, 3115A1-1120-US, 3115A1-1121-US, 3115A1-1117-US, Food Effect Study (3115A1-1116-US)	Proposed TBM only used in these 4 bioequivalence studies: (3115A1-1122-US, 3115A1-1139-US, 3115A1-1137-US, 3115A1-1142-US) Other studies using Formulation D: BA/BE Study (3115A1-1117-US) Multiple-Dose Study (3115A1-1138-US) BZA Polymorph Study (3115A1-1143-US)
Formulation Description	(b) (4)			

Abbreviations: BMD = bone mineral density; BR = Brazil; CE = conjugated estrogens; EU = European Union; PCP = Premarin current process; PNP = Premarin new process; US = United States; VMS = vasomotor symptoms; VVA = vulvar-vaginal atrophy; WW = world-wide.

Sponsor's Conclusions from Bioavailability/Bioequivalent Studies:

Study 3068A1-111-EU (Absolute Bioavailability):

Design: 3 mg IV vs 10 mg PO (BZA alone)
Conclusion: F=6% (absolute bioavailability)

Study 3115A1-102 (Effect of Food):

Design: 40 mg BZA/0.625 CE with or without high fat meal (PCP formulation, Formulation A (formulation used in Phase III studies 303 and 3307)
Conclusion: Increase Cmax (44%) and AUC (17%) with food

Study 3115A1-1116 (Effect of Food):

Design: 20 mg BZA/0.625 CE with or without high fat meal (PNP formulation, **Formulation C**
Conclusion: No change in Cmax, AUC increased by 25% with food

Study 3115A1-114 (PCP vs PNP):

Design: 20 mg BZA/0.625 CE (Formulation A vs Formulation B)
Conclusion: Failed

Study 3115A1-1120 (PCP vs PNP):

Design: 20 mg BZA/0.625 CE (Formulations C vs A), partial replicate design
Conclusion: Failed

Study 3115A1-1121 (PCP vs PNP), steady-state (14 days)

Design: 20 mg BZA/0.625 CE (Formulation A vs Formulation C)
Conclusion: Failed

Study 3115A1-1117 (A, B, C, and PNP): Clinical and commercial

Design: 20 mg BZA/0.625 CE (Formulation A, B, C, D-PCF (**PCF:** potential commercial formulation)
Conclusion:

D vs A failed
D vs B pass
D vs C Pass
B vs A pass
C vs A failed
C vs B pass

Study 3115A1-1122 (3 formulations vs A)

Design: Definitive BE study. (Formulation A vs **TBM, E, F, G**), 20 mg BZA/**0.625** CE
P.S. reformulated (b) (4)
Conclusion: A vs F passed for 20 mg BZA/**0.625** CE strength

Study 3115A1-1139 (B vs TBM)

Design: Definitive BE study. (Formulation B vs **TBM)**, 20 mg BZA/**0.625** CE
Conclusion: B vs F passed for 20 mg BZA/**0.625** CE strength

Study 3115A1-1137 (A vs TBM)

Design: (Formulation A vs **TBM, 1, 2, 3)**, 20 mg BZA/**0.45** CE
Conclusion: A vs TBM 2 passed for 20 mg BZA/**0.45** CE strength

Study 3115A1-1142 (B vs TBM)

Design: (Formulation A vs **TBM, 1, 2, 3)**, 20 mg BZA/**0.45** CE
Conclusion: B vs TBM 1 passed for 20 mg BZA/**0.45** CE strength

Summary of Formulation Bridging Studies;

Based on all BE studies, the following conclusions were made by the sponsor:

- Formulation A≠ C (Study 1120, 1121 and 1117 for 20/0.625mg strength)
- Formulation A= B (Study 1117 for 20/0.625mg strength)
- Formulation B = C (Study 1117 for 20/0.625mg strength)
- Formulation A = TBM (Study 1122 for 20/0.625mg strength)
- Formulation B = TBM (Study 1139 for 20/0.625mg strength)
- Formulation A = TBM (Study 1137 for 20/0.45mg strength)
- Formulation B = TBM (Study 1142 for 20/0.45mg strength)

In the clinical trial 304, patients initially receive formulation B and then switched to formulation C (20/0.45 and 0.625 mg) during the first 8 months of the first year and continued for the second year of the study. The endometrial safety/protection associated with lack of equivalency (18% lower exposure) of formulation C will be a review issue.

Reviewer's Comments:

The sponsor conducted extensive program [redacted] (b) (4) for this combination product. Many of the studies did not pass the bioequivalence criteria for BZA and/or CE components of the product at either Cmax or AUC levels.

The drug will be administered without regard of food. However, food appears to slightly increase exposure (pending review). The dosage and indications are as follows:

- Moderate to severe vasomotor symptoms: 20/0.45 or 20/0625 mg QD
- Moderate to severe vaginal atrophy: 20/0.625 mg QD
- Prevention of osteoporosis: 20/0.45 or 20/0625 mg QD

From the clinical pharmacology perspective, the following are some of the PK info of BZA:

- Half-life: ~30 h
- F= 6%
- Binding: 98-99%
- Excretion: Mainly in bile/feces and 1% in urine (radioactivity)
- Extensively metabolized: 4-fold increase in exposure in patients with hepatic impairment
- Metabolic Pathway: Glucuronidation is the major metabolic pathway
- Not recommended in patients with renal impairment.

Based on the above information and the known safety profiles of BZA, the exposure level will be carefully assessed in this NDA to optimize the chronic therapy with this product. From the clinical pharmacology perspective, there are three major challenges with this NDA as follows:

- Ensuring bridging of all formulations used in this NDA
- Factors that may lower BZA exposure and consistency in absorption. Lowering BZA exposure or reduce absorption may be associated with safety concern due to lack of adequate endometrial protection.
- Factors that may increase BZA exposure are also associated with both safety and efficacy issues. The increase in BZA exposure may reduce CE efficacy (VMS, VVA, and bone mineral density).

Therefore, consistency in BZA absorption, delivery, and systemic exposure appears to be critical in optimizing the long term therapy with this product.

Office of Scientific Investigations (OSI) Inspection:

No OSI inspection is necessary for the analytical and the clinical sites where the PK studies were conducted and blood samples analyzed. The reason for this decision is based on the favorable historical and recent inspections for these sites by OSI.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Comments to Sponsor's for 74-Day:

- Per the meeting minutes (Page 9) held on February 12, 2008, please submit to this NDA the audit report (b) (4) for the BZA/Atorvastatin drug interaction study (study # 3068A1-126-EU).
- Confirm that study # 3068A1-126-EU is the only study that was conducted (b) (4)
- Please provide the list of studies and their audits (if any) that were conducted or analyzed (b) (4)

Recommendation:

The NDA can be filed from the clinical pharmacology perspective.

Sayed (Sam) Al Habet, R.Ph., Ph.D.

Myong-Jin Kim, Pharm.D.
Secondary Reviewer Date

Appendix 1: List of Biopharmaceutics (Bioavailability and Bioequivalence) Studies

Type of Study (Location of CSR) Study Number and CSR Number	Study Objective(s)	Study Design and Type of Control	Test Product[a]; Dose Regimen; Route of Administration	Number of Subjects	Duration of Treatment[b]
Food-Effect Studies					
3115A1-102-US CSR-49949	Assess the effect of a high-fat meal on the relative bioavailability of BZA/CE; safety and tolerability.	Open-label, single-dose, randomized, 2-period crossover study.	BZA 40 mg/CE 0.625 mg fasting and after a high-fat meal. Oral	24	1 day
3115A1-1116-US CSR-69234	Assess the effect of a high-fat meal on the bioavailability of BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized-to-sequence, 3-period, crossover study.	BZA 20 mg/CE (PNP) 0.625 mg fasting or after a high-fat meal. BZA 20 mg/CE (PNP) 0.45 mg fasting. Oral	23	1 day
Comparative Bioavailability and Bioequivalence Studies					
3115A1-100-US CSR-45476	Compare the relative bioavailability of BZA and CE administered as separate tablets or as a combination-tablet formulation.	Open-label, single-dose, 3-treatment, 3-period, randomized crossover study.	BZA 10 mg x 4 and CE 0.625 mg BZA 10 mg/CE 0.625 mg BZA 40 mg/CE 0.625 mg Oral	24	1 day
3115A1-109-US CSR-62706	Assess the comparative bioavailability of 2 new formulations of BZA/CE (PNP) with BZA/CE (PCP) and with CE (PNP).	Open-label, single-dose, 4-period, crossover study.	BZA 40 mg/CE (PNP) 0.625 mg (b) (4) (Formulation B) BZA 40 mg/CE (PNP) 0.625 mg (b) (4) (Formulation B) BZA 40 mg/CE (PCP) 0.625 mg (Formulation A) CE (PNP) 0.625 mg Oral	24	1 day
3115A1-114-US CSR-67989	Assess the bioequivalence of BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized-to-sequence, 2 period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	72	1 day
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1117-US CSR-69737	Assess the bioequivalence of BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized, 4-period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation B) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) BZA 20 mg/CE (PNP) 0.625 mg (Formulation D [PCF]) Oral	76	1 day
3115A1-1120-US CSR-69235	Assess the bioequivalence between BZA/CE (PCP) and BZA/CE (PNP), assessing both the BZA and CE components.	Open-label, single-dose, randomized, 3-period, crossover study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	72	1 day

3115A1-1121-US CSR-69445	Assess subject exposure to BZA from 1 of 2 formulations of BZA 20 mg/CE 0.625 mg after steady-state administration.	Open-label, randomized, parallel inpatient/ outpatient study.	BZA 20 mg/CE (PCP) 0.625 mg (Formulation A) BZA 20 mg/CE (PNP) 0.625 mg (Formulation C) Oral	36 36	14 days
Comparative Bioavailability and Bioequivalence Studies (Continued)					
3115A1-1122-US CSR-75506	Assess the bioequivalence of clinical and commercial formulations of BZA/CE combination tablets.	Open-label, single-dose, randomized, 4-period, 4-treatment, crossover, bioequivalence inpatient/outpatient study.	BZA 20 mg/CE 0.625 mg (Formulation A - reference therapy). BZA 20 mg/CE 0.625 mg (Potential commercial formulation E - test formulation). BZA 20 mg/CE 625 mg (Potential commercial formulation F - test formulation). BZA 20 mg/CE 0.625 mg (Potential commercial formulation G – test formulation). Oral	82	1 day
3115A1-1137-US CSR-77978	Bioequivalence of test and reference formulations of BZA/CE combination tablets, assessing both the BZA and CE components.	Open-label, single-dose, randomized, 4-period, 4-treatment, crossover study.	BZA 20 mg/CE 0.45 mg (Formulation A-reference therapy) BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). Oral	90	1 day
3115A1-1139-US CSR-76333	Assess the bioequivalence of clinical and commercial formulations of BZA/CE combination tablets, assessing both the BZA and CE components.	Open-label, single-dose, randomized, 2-period, 2-treatment, crossover study.	BZA 20 mg/CE 0.625 mg (Formulation B - reference therapy). BZA 20 mg/CE 0.625 mg (proposed TBM formulation - test formulation). Oral	90	1 day
In Vitro/In Vivo Correlation Studies					
3115A1-115-US CSR-68097	Assess the bioavailability of BZA in 3 tablet release formulations of BZA/CE and an oral solution of BZA.	Open-label, single-dose, randomized, crossover study.	BZA 20 mg/CE 0.625 mg with the BZA component being: (b) (4) BZA 20 mg powder for oral solution Oral	24	1 day
3115A1-1123-US CSR-72948	Bioavailability of BZA/CE.	Open-label, single-dose, nonrandomized, 4-period, crossover study.	(b) (4) BZA 20 mg/CE 0.625 mg (b) (4) BZA 20 mg/CE 0.625 mg (b) (4) BZA 20 mg/CE 0.625 mg BZA 20 mg (oral solution) Oral	28	1 day

3115A1-1142-US CSR-78945	Assess the bioequivalence of 4 formulations of BZA/CE.	Open-label, single-dose, randomized, 4-period, crossover study.	BZA 20 mg/CE 0.45 mg (Formulation B – reference formulation). BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). Oral	88	1 day
3115A1-1143-US CSR-77979	Assess the bioavailability of 3 test formulations of BZA/CE (b) (4) (b) (4) compared with a potential market (reference) formulation of BZA/CE combination tablets, assessing only the BZA component.	Open-label, single-dose, randomized, 4-period, 4-treatment crossover study.	BZA 20 mg/CE 0.45 mg (test formulation 1). BZA 20 mg/CE 0.45 mg (test formulation 2). BZA 20 mg/CE 0.45 mg (test formulation 3). BZA 20 mg/CE 0.45 mg (PCF - reference therapy) Oral	37	1 day

Abbreviation: BZA=bazedoxifene; CE=conjugated estrogens; CSR=clinical study report; EU=European Union; IV=intravenous, PK=pharmacokinetics; PCP = Premarin current process; PNP = Premarin new process.

a. All test products were tablets unless otherwise specified.

b. Duration of treatment is the per protocol number of units of time (days, weeks, months, years) that individual subjects were exposed to the test article(s).

Source: Compounds (b) (4) Regulatory and Summaries/Summaries/Supporting Information/Bazedoxifene Conjugated Estrogens 2011 Table of all Clinical Studies

Appendix 2: List of Clinical Pharmacology Studies

Initial Safety, PK and PD	Drug Interactions	Drug Interactions	Exposure Response	ADME Biodistribution	Special Populations
SAD (3068A1-100-US)	Drug Interaction - Antacid (3068A1-102 FR)	**Drug Interaction-BZA/CE (3115A1-101-US)**	Population PK (3068A1-203-GL)	BZA ADME ^{14}C Radiolabel (3068A1-103-US)	Hepatic Disease (3068A1-112-EU)
MAD (3068A1-101-US)	Drug Interaction - Ibuprofen - (3068A1-106-SP)	**Drug Interaction-BZA on CE (3115A1-1134-US)**	Population PK (3068A1-300-GL)	BZA Absolute Bioavailability (3068A1-111-EU)	Age/Renal (3068A1-121-US)
BZA/CE Multiple Dose (3115A1-1138-US)	Drug Interaction - Azithromycin - (3068A1-125-EU)	**Drug Interaction-CE on BZA (3115A1-1135-US)**	QTc Study (3068A1-131-US)	BZA Dose Proportionality (3068A1-108-US)	SAD in China (3068A1-123-CI)
	Drug Interaction - Atorvastatin - (3068A1-126-EU)		Population PK (3115A1-303-US)	**BZA – BZA/CE Relative Bioavailability (3115A1-1136-US)**	SAD in Japan (3068A1-114-JA)
			Population PK (3115A1-304-WW)		MAD in Japan (3068A1-124-JA)

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; BZA = bazedoxifene; CE = conjugated estrogens; EU = Europe; FR = France; GL = global; JA = Japan; MAD = multiple ascending dose; PD = Pharmacodynamic; PK = Pharmacokinetic; QT_c = interval between the Q-wave and T-wave of the electrocardiogram, corrected; SAD = single ascending dose; US = United States; WW = worldwide

Note: Studies with the prefix 3068A1 were conducted with bazedoxifene monotherapy; studies with the prefix 3115A1 were conducted using BZA/CE. The studies conducted specifically for the BZA/CE development program are shown in **bold** font.

a. Four (4) studies listed in this figure were Phase 2 (3068A1-203-GL) or Phase 3 (3068A1-300-GL, 3115A1-303-US, and 3115A1-304-WW) studies that were used for population PK analyses.

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/s/

SAYED AL HABET
12/05/2012

MYONG JIN KIM
12/05/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	22-247
Submission Date	10/3/2012
Product name, generic name of the active	Bazedoxifene/ Conjugated Estrogens
Dosage form and strength	Tablet
Indication	Treatment of moderate to severe vasomotor symptoms due to menopause; treatment of moderate to severe vulvar and vaginal atrophy; prevention of postmenopausual osteoporosis.
Applicant	Wyeth
Clinical Division	DRUP
Type of Submission	505(b)(1) Original
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader (acting)	John Duan, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the dissolution test part of the DP specifications?	x		
2.	Does the application contain the dissolution method development report?	x		
3.	Is there a validation package for the analytical method and dissolution methodology?	x		
4.	Does the application include a biowaiver request?		x	Not Applicable.
5.	Is there information provided to support the biowaiver request?		x	Not Applicable.
6.	Does the application include an IVIVC model?	x		The Applicant has developed an IVIVC to support the proposed the dissolution acceptance criteria and to bridge the lower strength tablet to Formulation A and Formulation B, which were used in phase 3 studies (refer to Initial Assessment). Datasets are included in this submission.
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant claims that BZA is BCS class 2 (low solubility/high permeability) compound.

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8.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
9.	Is there any in *vivo* BA or BE information in the submission?	x		BA/BE Studies were conducted to 1) bridge commercial formulation with Formulation A and Formulation B, which were used in phase 3 studies (refer to Initial Assessment), 2) to develop IVIVC for the BZA/CE tablet, and 3) to develop IVIVR (b) (4) OCP will review the BA/BE studies.

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	Not Applicable.
12.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}
Kareen Riviere, Ph.D. — 11/29/2012
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
John Duan, Ph.D. — 11/29/2012
Biopharmaceutics Team Leader (acting) — Date
Office of New Drug Quality Assessment

Reference ID: 3223279

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

INITIAL ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

Bazedoxifene/Conjugated Estrogens (BZA/CE) tablets are a fixed dose combination produc (b) (4) A schematic of the development history of the BZA/CE commercial formulation is presented in Figure 1. The proposed to be marketed tablet strengths are 20 mg BZA/0.45 mg CE and 20 mg BZA/0.625 mg CE. (b) (4)

Figure 1. Development History of the BZA/CE Commercial Formulation

(b) (4)

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method, the proposed acceptance criteria for BZA and CE, an *in vitro in vivo* correlation (IVIVC) for BZA/CE tablets, and an *in vitro in vivo* relationship (IVIVR) (b) (4)

The proposed dissolution method:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	50 rpm	900 mL	37°C	Water with 0.1% SLS

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The proposed dissolution acceptance criteria:

Acceptance Criterion for BZA
NMT (b) (4) at 15 minutes
(b) (4) at 40 minutes
NLT (b) (4) at 60 minutes

Acceptance Criterion for CE
(b) (4) at 2 hours
(b) (4) (b) (4)
NLT (b) (4) at 8 hours

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed acceptance criteria for BZA and CE, 3) the IVIVR (b) (4) , and 4) the IVIVC to support the acceptance criteria and bridging the low strength BZA/CE tablet to the formulations used in the phase 3 clinical studies.

The ONDQA/Biopharmaceutics team has reviewed NDA 22-247 for filing purposes. We found this NDA **filable** from a Biopharmaceutics perspective.

Reference ID: 3223279

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/s/

KAREEN RIVIERE
11/29/2012

JOHN Z DUAN
11/29/2012