CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 22, 2013
From	Theresa Kehoe, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 022247
Applicant	Wyeth/Pfizer
Date of Submission	October 3, 2012
PDUFA Goal Date	October 3, 2013
Proprietary Name / Established (USAN) names	Duavee conjugated estrogens/bazedoxifene
Dosage forms / Strength	0.45 mg/20 mg tablet (0.45 mg conjugated estrogens/20 mg bazedoxifene) 0.625 mg/20 mg tablet (0.625 mg conjugated estrogens/20 mg bazedoxifene)
Proposed Indication(s)	1. Treatment of moderate to severe vasomotor symptoms associated with menopause 2. Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause 3. Prevention of postmenopausal osteoporosis
Recommended:	**Approval** for Duavee 0.45 mg/20 mg for • Treatment of moderate to severe vasomotor symptoms associated with menopause • Prevention of postmenopausal osteoporosis **Complete Response** for Duavee 0.625 mg/20 mg for • Treatment of moderate to severe vasomotor symptoms associated with menopause • Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause • Prevention of postmenopausal osteoporosis

1. Introduction

Wyeth Pharmaceutical, Inc., a wholly owned subsidiary of Pfizer, Inc., has submitted this New Drug Application (NDA) seeking to market two doses of the combination product conjugated estrogens and bazedoxifene (Duavee) for three indications 1) treatment of moderate to severe vasomotor symptoms associated with menopause; 2) treatment of moderate to severe vulvar and vaginal atrophy associated with menopause; and 3) prevention of postmenopausal osteoporosis. The conjugated estrogens 0.625 mg/bazedoxifene 20 mg dose is proposed for all three indications and the conjugated estrogens 0.45 mg/bazedoxifene 20 mg dose is proposed

for the vasomotor symptoms and prevention of osteoporosis indications. Five Phase 3 trials are submitted in support of these indications and will be the focus of this review.

2. Background

Duavee is a combination product consisting of conjugated estrogens and bazedoxifene, an estrogen agonist/antagonist (also referred to as a selective estrogen receptor modulator or SERM). Conjugated estrogens (Premarin) has been marketed in the U.S. since 1942. Under the Drug Efficacy Study Implementation (DESI) process, conjugated estrogens were determined to be "effective" for menopausal symptoms and "probably effective" for selected cases of osteoporosis (July 25, 1972). The menopausal symptoms indication was later reworded to moderate to severe vasomotor symptoms associated with menopause, atrophic vaginitis, and kraurosis vulvae (September 29, 1976).

After publication of the findings of the Women's Health Initiative Study, significant labeling changes occurred for all approved estrogen and combination estrogen/progestin products. The most recent recommendations for labeling are outlined in the 2005 draft guidance "*Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling"*. Recommended labeling includes language for Boxed Warnings, Indications, Contraindications, Warnings and Precautions, Adverse Reactions, Pregnancy, Nursing Mothers, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Clinical Pharmacology, and Clinical Studies.

Bazedoxifene is not an approved product in the US.

Guidance documents used by the Applicant during product development include the 1995 FDA Hormone Replacement Therapy Working Group *"Guidance for clinical evaluation of combination estrogen/progestin-containing drug products used for hormone replacement therapy of postmenopausal women"*. In 2003, this was replaced with the current draft guidance *"Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations of Clinical Evaluation"*

The phase 2 dose-finding study for the conjugated estrogens/bazedoxifene combination was conducted outside of the IND. An End-of Phase 2 meeting was held with the Applicant in July, 2001. The first Phase 3 trial 3115A1-303 was begun in April, 2002. The second phase 3 trial, 3115A1-304 was the subject of a Special Protocol Assessment in 2005. Agreement was reached in that Trial 304 would be the confirmatory endometrial safety study with demonstration of an incidence rate of endometrial hyperplasia of ≤ 1% with the upper bound of the 95% confidence interval ≤ 4%. Trial 3115A1-304 was begun in October 2005. Trial 3115A1-305 served as the primary trial supporting the vasomotor symptom indication began in September, 2005 and was not conducted under a Special Protocol Assessment. Similarly, Trial 3115A1-306 began in October, 2005 and serves as the primary trial supporting the vulvar and vaginal atrophy indication. The preNDA meeting for this application was held July 18, 2007. After that meeting, it became apparent to the Applicant that the confirmatory

endometrial safety study, Trial 3115A1-304 utilized a drug product formulation that was not bioequivalent to the formulation used for Trial 3115A1-303. In addition, an unacceptable rate of endometrial hyperplasia was found. The Applicant postponed the NDA submission and submitted a new trial to replace Trial 3115A1-304. Trial 3115A1-3307 was submitted as a Special Protocol Assessment in August, 2008. The Applicant sought agreement that 3115A1-3307 would be acceptable as a replacement for Trial 3115A1-304. Following a "No Agreement" letter, a teleconference was held with the Applicant in December 2008 at which time agreements were reached on the design of Trial 3115A1-3307.

Additional meetings were held in February, 2010 (CMC Pre-NDA) and September 27, 2011 (Administrative). In addition, a Type C meeting with the Division and the Office of Scientific Investigations was held September 14, 2012, to discuss the amount of missing data and incomplete retention of records associated with the trials supporting the proposed indications.

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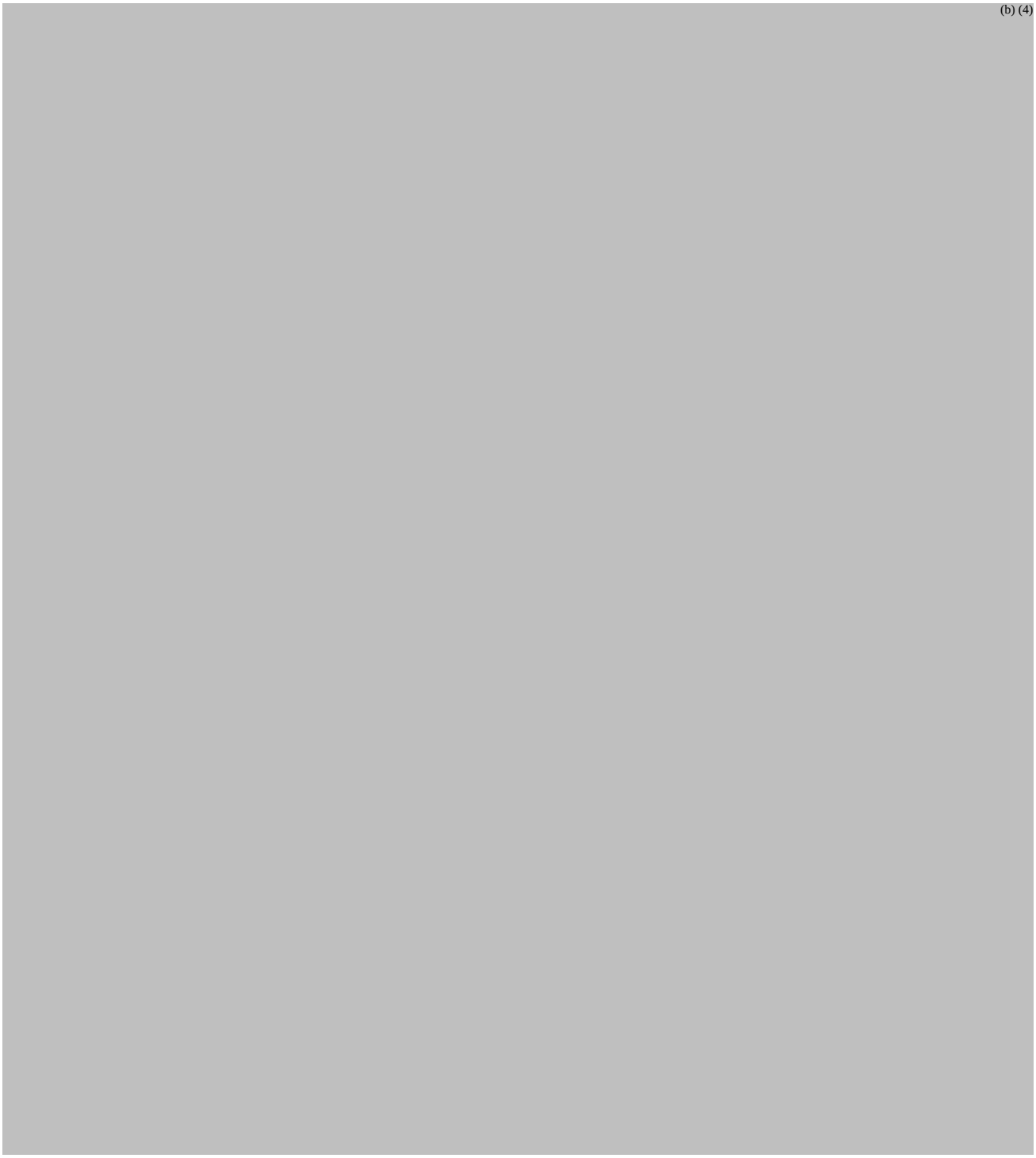


This marketing application for conjugated estrogens/bazedoxifene combination product is part of the PDUFA V Program. A mid-cycle communication teleconference was held with the Applicant on March 20, 2013 and the following issues were communicated and discussed:

1. We have concerns regarding the high number of study subjects with absence of source documentation, especially the high number of subjects with complete absence of source documentation. This will be taken into account as we evaluate efficacy and safety.

2. [redacted] *We are closely evaluating intrinsic and extrinsic factors that may potentially affect the pharmacokinetic (PK) characteristics of bazedoxifene and in particular the exposure, metabolism, and formulation performance.*

3. We note multiple formulations used in the development program for conjugated estrogen/bazedoxifene and the difficulty in finding to-be-marketed formulations that are bioequivalent to the formulations used in the clinical trials. The formulation changes and rationale for new formulation development are not clear (see our information request below).

4. The following Quality issues were conveyed in a letter dated March 18, 2013.

- *Updated information is required for the manufacturing process, packaging operations and hold times for bulk tablets.*
- *Specifications should be included* [redacted] *in the drug product and additional supporting documentation provided to support the acceptance criteria. Specifications and Stability Commitment should be updated.*
- *The acceptance criteria for the bazedoxifene dissolutions should be modified and specifications updated.*
- *An Environmental Assessment should be submitted for both active pharmaceutical ingredients (APIs).*

A Late-Cycle Meeting was held with the Applicant on June 26, 2013. The following deficiencies were conveyed and discussed:

1. [redacted] *dissolution failures discovered during the drug product manufacturing site inspection and the Method Validation performed at the St. Louis laboratory*

2. Environmental Assessment has not been adequately prepared. In order to allow for compliance with the EA requirements to support approval of this NDA in this cycle, you should submit a literature-based EA for conjugated estrogens, using data available on estrogens, estradiol equivalents and exposure models, in order to assess the risks to ecological species associated with this application. The EA can be updated in 2015 once the planned studies are completed.

3. A test and acceptance criterion for [redacted] *bazedoxifene in the drug product is needed*

4. Facilities inspections have been completed and the final recommendation is pending at this time

5. Inadequate information currently available related to bridging all formulations to the final to-be-marketed formulation

6. [redacted]

7. [redacted]

8. Content and reliability of data from Trial 303

In response to the discussions and agreements at the Late Cycle Meeting, the Applicant submitted additional information to the application on July 31, 2013. The information submitted appears to address the main approvability issues.

3. Chemistry, Manufacturing, and Controls

The Duavee drug product development program has encountered challenges. Please see Dr. Christner and Shafiei's review for complete details. Two dose strengths (0.625 mg conjugated estrogens/20 mg bazedoxifene and 0.45 mg conjugated estrogens/20 mg bazedoxifene) for Duavee have been developed. There have been multiple formulations developed from the first formulation used in clinical trials to the final to-be-marketed formulation. The initial CMC review for this NDA recommends that the data provided are not adequate for approval. Numerous CMC issues were presented and discussed with the Applicant at the Late Cycle Meeting. The Applicant provided an in depth response on July 31, 2013. In the ONDQA review addendum, the Applicant has satisfactorily addressed all of the deficiencies and the application is now acceptable for approval from ONDQA's perspective.

General product quality considerations:
The conjugated estrogens drug substance is a mixture of water-soluble sodium estrone, equilin sulfates, and other estrogenic substances extracted from the urine of pregnant mares. Full drug substance information is cross-referenced to the approved conjugated estrogens monotherapy product Premarin (NDA 004782). [redacted] The drug substance is currently approved with a retest period of [redacted] months.

[redacted] The synthetic process for bazedoxifene acetate and description of commercial manufacturing processes for bazedoxifene acetate is provided in DMF [redacted]. This DMF has been reviewed and has been found to be adequate to support this NDA. Based on the review of the drug substance information provided, the bazedoxifene acetate drug substance manufactured by [redacted] is acceptable for use in the manufacture of the Duavee drug product with a retest period of [redacted] months when the drug substance is stored [redacted]

The Duavee drug product is an oval, biconvex, film-coated tablet [redacted]

(b) (4) Further formulation development ensued until the final formulation, bioequivalent to both Formulation A and Formulation B for conjugated estrogens and bazedoxifene was found.

The to-be-marketed conjugated estrogens 0.45 mg/ bazedoxifene 20 mg tablets are pink with black branding on one side (b) (4)

Stability and testing criteria include an acceptable dissolution method, an acceptable HPLC analysis method for conjugated estrogens dissolution samples, and an acceptable UV analysis method for bazedoxifene dissolution samples. Dissolution acceptance criteria for conjugated estrogens are (b) (4) at 2 hours, (b) (4) at 3 hours and no lower than (b) (4) at 8 hours. For bazedoxifene, the agreed upon acceptable dissolution criteria are no more than (b) (4) at 15 minutes and no less than (b) (4) at 8 hours.

The *In Vitro In Vivo Correlation (IVIVC)* for the conjugated estrogens/bazedoxifene tablets was not acceptable. Comments were conveyed to the applicant for the Late Cycle meeting and it was recommended that the Applicant build an *IVIVC* model using the conjugated estrogens/ bazedoxifene acetate tablet data, validate the model, and show the robustness of the model. In the submission dated 7/31/2013, the Applicant responded that they do not intend to pursue the IVIVC model to support tablet testing. Please refer to Dr. Riviere's and Dr. Duan's reviews for complete details.

The Applicant provided data (b) (4) This deficiency was conveyed to the Applicant

[1] The Executive Summary of Dr. Christner's review states (b) (4) After discussion with Dr. Christner, this is a typographical error (b) (4)

prior to and at the Late Cycle Meeting. The Applicant proposed testing and specifications for bazedoxifene [redacted] is acceptable per the Office of New Drug Quality Assessment.

A change in the supplier [redacted] for the to-be-marketed drug product resulted in a drug product [redacted] Wyeth/Pfizer plan to mitigate the risk [redacted] In the data submitted July 31, 2013, the release testing and 3 month stability data on the confirmatory batches met the acceptance criteria (level 1) for both bazedoxifene and conjugated estrogens dissolution [redacted] please see Dr. Vipul Dholakia's review for compete details.

Packaging for the tablets [redacted]: [redacted] a blister package consisting of two blisters of 15 tablets each which are packaged in an aluminum pouch. The container closure systems are packaged [redacted] The drug product is labeled with instructions to keep the tablets in the container closure system and to use within [redacted] 60 days (for blisters) after opening.

An expiration dating period has been set at 36 months for the Duavee 0.45/20 drug product [redacted].

Facilities review/inspections
The bazedoxifene acetate drug substance is manufactured [redacted]. An inspection was held in [redacted] and the site is Acceptable. [redacted] This facility is Acceptable based on profile.

The conjugated estrogens drug substance is manufactured at Pfizer Canada, Brandon, Manitoba. This site has an Acceptable recommendation from the Office of Compliance.

The Duavee finished drug product is manufactured and tested at Pfizer, Ireland Pharmaceuticals, County Kildare, Ireland. This site also packages the final drug product into blister configuration. An inspection was performed at the Pfizer Ireland facility in February 2013. As outlined in the Establishment Inspection Report, pages 188-189 of the CMC review, during the inspection dissolution failures were noted [redacted]

[redacted] At the time of inspection, a confirmation batch was in progress. The District Office has recommended a WITHHOLD pending further information. Issues regarding the Pfizer Ireland inspection findings, the dissolution failures, and [redacted] the finished drug product were discussed at the Late Cycle Meeting. Further data addressing the inspectional issues were submitted on July 31, 2013. The final recommendation from the Office of Compliance on 8/14/13 is Acceptable.

The final Duavee drug product is packaged [redacted]. This facility is Acceptable based on profile.

Environmental Assessment

[redacted]

Environmental Assessments (EA) for both bazedoxifene and for conjugated estrogens are required for approval of this NDA. Please see Dr. Jim Laurenson's review and review addendum for complete details. The rationale for this approach is based on the fact that both conjugated estrogens and bazedoxifene are hormonally active substances and hormonally active substances have the potential for harm to the environment at the expected level of exposure. A request for an Environmental Assessment was conveyed to the Applicant on March 18, 2013. The Applicant proposed [redacted] which is not acceptable under current regulations. Issues surrounding the EAs were discussed at the Late Cycle Meeting. The Applicant submitted environmental assessments for bazedoxifene and for conjugated estrogens on July 31, 2013. Upon review, it is determined that approval of the NDA for Duavee (conjugated estrogens/bazedoxifene) is not expected to have a significant impact on the human environment (a finding of no significant impact [FONSI]).

Status of Deficiencies

As discussed in the paragraphs above, at the time of the Late Cycle meeting, the following deficiencies precluding approval of Duavee were communicated to the Applicant:

1) Specifications [redacted] need to be included in the commercial stability studies.
2) The [redacted] phenomenon discovered during inspection and method validation studies needs to be addressed before an expiration dating period can be granted.
3) Environmental Assessments for both bazedoxifene and conjugated estrogens need to be submitted.

4) A final Acceptable recommendation from the Office of Compliance for the Pfizer Ireland facility is needed.
5) Labeling needs to be agreed-upon and finalized.

The Applicant addressed these deficiencies in the June 5 and July 31 submissions to the NDA and their response has been found acceptable. The Applicant's labeling response was submitted August 16, 2013 and final labeling remains pending at the time of completion of this review.

4. Nonclinical Pharmacology/Toxicology

The nonclinical data provide support approval of both doses of the conjugated estrogens/bazedoxifene combination tablet. Please see Dr. Leslie McKinney's review for complete details. Conjugated estrogens have been marketed since 1942 under NDA 004782 and specific nonclinical studies for conjugated estrogens are not included in this NDA.

(b) (4)

Conjugated estrogens exert biologic activity by binding to both the alpha and beta forms of the estrogen receptor (ER-α and ER-β) located in the nuclei of target tissues. Bazedoxifene is a selective estrogen agonist/antagonist that also binds to ER-α and ER-β. It acts as an estrogen agonist in bone and as an antagonist in the uterus and breast. Similar to estrogens, bazedoxifene alone increases the risk of venous thrombosis. Unlike estrogens, bazedoxifene alone increases vasomotor symptoms. The interaction and effects of bazedoxifene relative to estrogen in each tissue is variable.

Pharmacological characterization of the conjugated estrogens/ bazedoxifene combination include in vitro mechanistic studies and in vivo nonclinical studies designed to determine whether co-administration of the two compounds, both acting at the same receptor, would lead to toxicity different from that observed with each alone.

The effect of bazedoxifene alone and the conjugated estrogens/bazedoxifene combination on bone parameters was evaluated in a one year ovariectomized rat study. Estrogen loss following ovariectomy in rats produces a loss of bone mineral density. This loss is prevented by administration of exogenous estrogen. As outlined in Figure 1 below, administration of bazedoxifene alone to ovariectomized rats partially prevented the bone loss at both the lumbar spine and right proximal femur. Administration of the conjugated estrogens/bazedoxifene combination had similar effects to administration of estrogens alone. Similar effects were seen with other parameters including biomechanical testing – exogenous estrogens alone and in combination with bazedoxifene maintained bone strength and bazedoxifene alone partially maintained bone strength.

Figure 1: Mean (SE) percent change from baseline in BMD (g/cm2) by DEXA at the lumbar spine and right proximal femur (Fig 5A and 5B, Komm et al., 2011)
Source: page 18, Pharmacology / Toxicology Review

The effect of bazedoxifene alone and the conjugated estrogens/bazedoxifene combination on vasomotor symptoms was evaluated in a rat model of vasomotor instability. In this model, ovariectomized, morphine-addicted rats are given a bolus injection of naloxone that induces a rapid thermoregulatory response detected as an increase in tail skin temperature. Administration of conjugated estrogens (10 mg/kg) was effective in suppressing the change in tail skin temperature. Bazedoxifene partially opposed the effect of estrogen when tested over the range 0.1-10 mg/kg, without a clear dose response.

The ability of bazedoxifene to oppose the estrogen-induced increase in uterine wet weight was evaluated in a three-day immature rat uterine model. One study utilized ethinyl estradiol as the estrogen component and a second study used conjugated estrogens. Both studies demonstrated that bazedoxifene inhibited the estrogen-induced increase in uterine wet weight in a dose-dependent manner. On histologic evaluation, bazedoxifene prevented ethinyl estradiol-induced myometrial and luminal cell hypertrophy.

A mouse model of femoral vein thrombosis was developed to evaluate the effect on bazedoxifene on the time course for formation of venous thrombosis. As discussed in Dr. McKinney's review, changes in time to occlusion were small for all groups with the only significant time decrease occurring in the conjugated estrogens/medroxyprogesterone group. This makes interpretation of these results difficult, especially in light of what is known about clinical VTE events where increases in the number of events is seen with both estrogen and bazedoxifene monotherapy.

Bazedoxifene alone was negative in safety pharmacology studies and had no significant off-target activity at other steroid receptors. Weak cross-reactivity was reported at the sigma opioid receptor, the only positive finding from screening assays against a standard panel of

receptors. No safety pharmacology studies were conducted with the conjugated estrogen/bazedoxifene combination.

The pharmacokinetics and metabolism of bazedoxifene alone were characterized in multiple species. Bazedoxifene is well absorbed and its bioavailability appears limited by first pass metabolism. Glucuronidation is the major metabolic pathway. The primary route of excretion is biliary / fecal. There is no significant induction of hepatic enzymes and the potential for drug-drug interaction is low. For the conjugated estrogens/ bazedoxifene combination, one in vitro study was conducted to examine potential metabolic interactions between the two compounds. Bazedoxifene and conjugated estrogens do not appear to alter the pharmacokinetics or metabolism of one another.

In toxicology studies with bazedoxifene alone, findings in ovariectomized rat and monkeys suggest a potential for estrogen-like functional or histologic changes in uterus, cervix and vagina.

Toxicology studies with the conjugated estrogen/bazedoxifene combination include a 30 day study in female rats, a 6 month study with 3 month recovery phase in female rats, a 30 day study in female monkeys, and a 9 month study in female monkeys. In vitro characterization utilizing various gene expression, cofactor interaction, and functional assays in a number of different cell types support the conclusion that the combination of conjugated estrogens and bazedoxifene will result in tissue responses that are different from either conjugated estrogens or bazedoxifene alone and different for each tissue type.

In female rats, estrogen associated expected changes in clinical chemistry (increased T4 and decreased cholesterol) were observed. Decreases in pituitary and adrenal glands weights occurred without microscopic findings. These findings are similar to what was seen in studies with bazedoxifene alone indicating that the addition of estrogen did not diminish the effects of bazedoxifene on the pituitary or adrenal glands. Uterine weight decreased in all treatment groups, and correlated microscopically with uterine atrophy indicating that the addition of bazedoxifene to estrogen negated the expected hypertrophic effect of estrogen on the uterus. Bazedoxifene alone also causes reduced uterine weight and atrophy. Effects on the ovary were mixed. Ovarian weight was generally decreased across all groups, which is consistent with the known effects of estrogen in that estrogen stimulation causes ovarian atrophy and decreased ovarian weight. Cystic follicles were also present in all treatment groups, and in the high dose bazedoxifene/conjugated estrogens group correlated with increased ovarian weight. In previous rat studies, bazedoxifene alone caused increased ovarian weights and cystic ovarian follicles. Mammary gland lobular hyperplasia occurred in a few animals in the mid- and high-dose bazedoxifene/ethinyl estradiol group. Mammary gland lobular hyperplasia was not previously observed with bazedoxifene alone.

In female monkeys, 30 days of therapy with 0.6/15, 2/50, or 6/150 mg/kg ethinyl estradiol /bazedoxifene or 0.2/15, .066/50, or 2/150 mg/kg conjugated estrogens /bazedoxifene daily resulted in no mortality, no treatment-related clinical findings, and no reported toxicologically significant changes in hematology or clinical chemistry. Mean ovarian weight increased and was associated with cystic follicles. Uterine weight decreased and was associated with atrophy.

Cervical and vaginal atrophy were also noted. Decreased adrenal and pituitary weights were not dose-related and did not have associated microscopic findings. The 9 month monkey study utilized daily conjugated estrogens/bazedoxifene doses of 0.1/7.5, 0.45/33.5, and 2/150 mg/kg. There was no mortality and there were no significant clinical findings. The doses of conjugated estrogens/bazedoxifene administered resulted in increased ovary and decreased uterine weights at all doses that were accompanied by microscopic findings of cystic follicles and atrophy, respectively. Liver weight was modestly increased, without microscopic findings. Changes in the ovary and uterus are expected pharmacologic effects and are consistent with the findings in the other studies in the rat and monkey.

Genetic toxicology

Bazedoxifene alone was negative for genotoxicity in the standard battery of in vitro and in vivo genotoxicity assays. Genotoxicity of the conjugated estrogens/bazedoxifene combination was not evaluated.

Carcinogenicity

Carcinogenicity potential of bazedoxifene alone was evaluated in a 2-year rat study and in two 6-month Tg.rasH2 studies (b) (4) Carcinogenicity for the combination conjugated estrogens and bazedoxifene was not evaluated. With bazedoxifene alone, there was a dose-related increase in benign ovarian granulosa cell tumors in intact non-ovariectomized rats with significant incidence of tumors noted at 2.6x and 6.6x the clinical 20 mg bazedoxifene dose based on AUC of the parent compound. Although these tumors are likely due to an indirect stimulatory effect of gonadotropins released as a result of a central anti-estrogenic action of bazedoxifene, direct stimulation of the ovary cannot be excluded. Ovarian tumors have been observed in all SERM carcinogenicity studies.

In the rat, survival was increased due to a reduced incidence of pituitary tumors in males and of pituitary and mammary tumors in females in all dose groups. Renal tumors were observed in male rats. The clinical relevance of these tumors is also not known. The tumor type has been seen with other SERMs and is believed to be rodent-specific.

Reproductive Toxicity

Fertility (Segment 1) and embryofetal (Segment 2) toxicity studies were conducted in the rat and rabbit with bazedoxifene alone (b) (4) Reproductive toxicity for the combination conjugated estrogens and bazedoxifene was not evaluated. In the rat, bazedoxifene had no effect on male fertility but interfered with estrous cycling, fertility, and ability to maintain pregnancy in females. In both the rat and rabbit, maternal toxicity (reduced body weight and consumption) was observed in pregnant dams at all doses, along with reduced implantation (rat) or increased abortion (rabbit) and fetal survival. Major malformations were not observed, but vascular abnormalities, delayed ossification, and enlarged thyroid were reported. NOAELs for all of the reproductive toxicity studies were at or below the lowest administered dose, and were less than 1x the human AUC at the proposed therapeutic dose. These data indicate that bazedoxifene poses a risk to women who are or may become pregnant. The Applicant has proposed a Pregnancy category X in labeling.

Other Issues:
Degradation of the bazedoxifene acetate drug substance results in four potential impurities. As outlined in Dr. McKinney's review, none have structural alerts, two have been qualified, and two did not require qualification.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology data provide support for approval of the 0.45 mg conjugated estrogens/20 mg bazedoxifene dose. Please see the Clinical Pharmacology review and review addendum for complete details. In total, the Applicant conducted 35 clinical studies detailing the clinical pharmacology and biopharmaceutics of the conjugated estrogens/bazedoxifene combination. Most of the studies investigated the bazedoxifene monotherapy product while other studies specifically evaluated the combination of conjugated estrogens and bazedoxifene including one study that looked at the interaction of bazedoxifene on conjugated estrogens and a second that assessed the interaction of conjugated estrogens on bazedoxifene. Because of the difficulties encountered in formulation development, multiple bioequivalence studies were required to assess the new potential formulations.

General Clinical Pharmacology:
The absolute bioavailability of bazedoxifene alone is approximately 6% with a mean Cmax of 6.2 ng/mL and Tmax of 1.7 hours at steady state. The bazedoxifene half-life at steady state is approximately 30 hours. At steady state, the Cmax and AUC of bazedoxifene are approximately twice that of single dose values (Figure 2.2.4.1.1, page 22 of the Clinical Pharmacology QBR review). Similar increases in Cmax and AUC at steady state compared to single dose were achieved for both the bazedoxifene component and the unconjugated estrone component of the combination conjugated estrogens/bazedoxifene tablet. The pharmacokinetic profile of bazedoxifene is dose-proportional for oral single doses from 2.5 to 120 mg and for oral multiple daily doses from 5 to 80 mg. A high fat meal increases bazedoxifene AUC by approximately 27%.

Studies evaluating the effect of bazedoxifene and conjugated estrogens on the pharmacokinetics of the other component in the combination were conducted. In study 3115A1-1135, conjugated estrogens did not significantly affect bazedoxifene exposure. In study 3115A1-1134, bazedoxifene did not significantly affect bazedoxifene exposure of unconjugated estrone, baseline-adjusted unconjugated estrone, total estrone, baseline-adjusted estrone, unconjugated equilin, or total equilin.

Bazedoxifene is 95.8 – 99.3% plasma protein bound. Bazedoxifene is extensively metabolized in the liver to phenyl and indole glucuronides by microsomal uridine diphosphate-glucuronosyltransferase isoenzyme A1 (UGT1A1) and uridine diphosphate -glucuronosyl transferase isoenzyme A10 (UGT1A10). There is little or no oxidative metabolism. The indole glucuronide is the major circulating metabolite, whereas the phenyl and diglucuronides are the minor metabolites in plasma. The indole metabolite may contribute to 6.7-9.5% of bazedoxifene *in vivo* antagonistic activity at the receptors. The ratios of plasma indole glucuronide concentration to plasma bazedoxifene concentration are about 11.7-16.6.

Drug-Drug Interactions:
Bazedoxifene does not affect the plasma protein binding of warfarin, diazepam, or digoxin. Similarly, warfarin, diazepam, and digoxin do not affect bazedoxifene plasma protein binding. Bazedoxifene and ibuprofen pharmacokinetics are not significantly altered with co-administration of single oral doses of these two drugs. There was no noticeable interaction between bazedoxifene and atorvastatin. A single dose of antacids containing 460 mg aluminum hydroxide and 400 mg magnesium hydroxide did not have an effect on a single oral 40 mg bazedoxifene dose. The AUC of bazedoxifene is decreased by 15% in the presence of oral azithromycin 250 mg.

No specific drug-drug interaction studies have been done with uridine diphosphate-glucuronosyltransferase inducers (such as, rifampin, phenobarbital, carbamazepine, phenytoin) or inhibitors (such as, gemfibrozil, ketoconazole). As part of study 3068A1-106 which evaluated the pharmacokinetics of bazedoxifene administered alone or with ibuprofen, analyses were done to determine if there was any correlation between UDP-glucuronosyl transferase isoenzyme A1 (UGT1A1) genotype and the pharmacokinetic characteristics of bazedoxifene. Subjects were genotyped for UDP-glucuronosyl transferase isoenzyme A1 (UGT1A1) and classified as an extensive or poor metabolizer. There was no apparent correlation between genotype and bazedoxifene pharmacokinetics.

Intrinsic Factors / Special Populations:
Age: The effect of age on the pharmacokinetics of bazedoxifene alone was assessed in an open-label study of postmenopausal women. Subjects were stratified and defined as young-elderly (51-64 years, n=8), mid-elderly (65-74 years) group and elderly (> 75 years). Compared to 51-64 years old, bazedoxifene increased 54% in the 65-74 year age group and 158% in the >75 year age group. For the 65-74 year age group, Cmax and half life were similar to subjects 51-64 year age group. In the > 75 year age group, Cmax increased 34% and bazedoxifene half-life increased from a mean of 32 hours to a mean of 46 hours. Based on the increased exposure to bazedoxifene noted in this trial and the lack of subjects over age 75 years enrolled in the Duavee clinical trials, the Clinical Pharmacology team believes that use of Duavee in patients over age 75 years is not recommended.

Race: Race does not appear to affect the pharmacokinetics of bazedoxifene.

Weight: (b) (4)

To evaluate this concern, an analysis of the effect of weight on bazedoxifene exposure was conducted by the clinical pharmacology/pharmacometrics team using the dense PK database (n=237). The population PK analysis of dense PK data indicated that bazedoxifene 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 bazedoxifene exposure is expected in this group of patients.

Renal Impairment: A specific renal impairment study was not conducted. Data from postmenopausal patients (n = 2) with severe renal impairment (CrCl < 30 mL/min) is presented. In these two patients, bazedoxifene AUC increased 69% compared to that of 8 healthy postmenopausal women (51-64 years) when they received a 20 mg single oral BZA dose. The Clinical Pharmacology reviewers have concluded that these limited data do not provide definitive conclusions regarding the effect of renal impairment on bazedoxifene exposures.

Hepatic Impairment: The effect of hepatic function on the pharmacokinetics of bazedoxifene alone was assessed in an open-label study of postmenopausal women. The degree of hepatic impairment was defined using the Child Pugh classification (A, B, or C). Subjects with mild, moderate, and severe hepatic impairment showed a 143%, 109%, and 268% increase, respectively, in bazedoxifene AUCs as compared to that for healthy subjects. The half-life of bazedoxifene was also prolonged from 32 hours to 50 hours in subjects with severe Child Pugh Class C disease. No hepatic impairment studies were done for the Duavee combination product. Based on the clinical data, it is clear that increasing bazedoxifene exposure reduces the beneficial effects of estrogen for vasomotor symptoms and bone mineral density increases. In the clinical trials, patients with hepatic impairment were excluded from the studies. Therefore there is an absence of data on the clinical safety and efficacy of Duavee in patients with liver impairment.

The Applicant proposes to contraindicate the use of Duavee in patients with liver dysfunction or disease. The Clinical Pharmacology team agrees that Duavee is not recommended for use in patients with hepatic impairment and the labeled contraindication.

QT Assessment:
Concerning QT prolongation has been found with other estrogen agonist/antagonists (toremifene). A thorough QT study was conducted for bazedoxifene monotherapy and reviewed by the Interdisciplinary Review Team for QT Studies (b) (4) Utilizing doses of bazedoxifene up to 120 mg, the thorough QT study was negative. This would cover accumulation at steady state, accumulation in hepatic impairment patients (based on Cmax only, not AUC) and is expected to cover accumulation in the presence of a UGT inhibitor.

Bioequivalence and Bridging of the To-Be-Marketed Product:
Two formulations (A & B) were used in the main clinical trials supporting the three indications sought for Duavee. A third formulation, C, was also used in clinical trials but was not bioequivalent to Formulation A. Formulation C provides important safety information for the proposed combination product and will be discussed in depth in the clinical sections of this review. Due to the (b) (4) issue with Formulation B and the lack of bazedoxifene bioequivalence with Formulation C, additional formulation development occurred to find the to-be-marketed formulation. In the original application submission, the review team found it difficult to trace the formulation development and to assure that bioequivalence had been demonstrated between the final to-be-marketed combination drug product and the formulations

used in the clinical trials. Some of this confusion resulted from changes in the terminology used for the various product formulations – formulations A through G with Formulation D having versions 1, 2, and 3, and a final version of formulation F renamed to Formulation CF. An information request was sent to the Applicant on March 21, 2103. The response submitted April 5, 2013, was insufficient to answer the questions raised and a second information request was sent to the Applicant May 24, 2013. On June 18, 2013, the Applicant submitted their response. Formulation bridging was also discussed at the Late Cycle Meeting. In their response, the Applicant made clear that Formulation CF represented the final commercial formulation. (b) (4) The to-be-marketed formulation (Formulation CF) 0.45mg/20mg dose was demonstrated to be bioequivalent to Formulation A 0.45mg/20mg in study 3115A1-1137-US. The to-be-marketed formulation (Formulation CF) 0.45mg/20mg dose was demonstrated to be bioequivalent to Formulation B 0.45mg/20mg in study 3115A1-1142-US. The (b) (4) issues noted in the commercial stability batches and the Applicant's response (b) (4) did not result in changes in the Duavee product formulation. Because the formulation has not changed, further bioequivalence testing is not needed.

Bioanalytical Methodologies:
The methodologies for the analysis of both conjugated estrogens and bazedoxifene are well validated and established. The analytical methods for conjugated estrogens evaluated 16 estrogen components, as outlined in Table 9, page 14 of the Clinical Pharmacology review addendum. Solid phase extraction was used to analyze unconjugated estrone, equilin, Δ8,9-dehydroestrone, 17β-estradiol, 17β-dihydroequilin, and 17β-Δ8,9-dehydroestradiol; while enzymatic hydrolysis with solid phase extraction was used to measure the other components. These methods are well established and validated for conjugated estrogens. The analytical method for bazedoxifene utilizes high performance liquid chromatography (HPLC)-fluorescence and liquid chromatography/tandem mass spectrometry. The lower limit of quantitation was 25 pg/mL with a linear range of 25-2500 pg/mL.

The Applicant reported that the bazedoxifene monotherapy atorvastatin interaction study 3068A1-126-EU is the only study for this NDA that was conducted (b) (4) Audit reports were previously submitted, reviewed and found acceptable. The Applicant also reported that only one study was associated with (b) (4) during the period (b) (4) For study 3068A1-131-US (the thorough QT study), moxifloxacin plasma concentrations were measured (b) (4). The findings of this study are not impacted by the positive control measurements performed (b) (4)

6. Clinical Microbiology

There are no Clinical Microbiology issues pertinent to the NDA.

7. Clinical/Statistical- Efficacy

The Applicant is seeking three indications for conjugated estrogens/bazedoxifene. Each indication will be discussed separately. Both the conjugated estrogens 0.625 mg/bazedoxifene 20 mg (0.625/20) dose and the conjugated estrogens 0.45 mg/bazedoxifene 20 mg (0.45/20) dose are proposed for the vasomotor symptoms and the prevention of osteoporosis indications. For the vulvar and vaginal atrophy indication, (b) (4) only the 0.625/20 dose is proposed. Five main efficacy trials are included in the application. Trial 3115A1-305 is the main trial for the vasomotor symptoms indication, with supportive evidence from endpoints in trial 3115A1-303. Trial 3115A1-306 is the main trial for the vulvar and vaginal atrophy indication. For prevention for postmenopausal osteoporosis, Trial 3115A1-303 is the main trial with supportive evidence from Trial 3115A1-3307.

Both conjugated estrogens and bazedoxifene exert their effect through the estrogen receptor. In this combination product, bazedoxifene replaces a progestin to provide endometrial protection. At the uterus, bazedoxifene clearly has estrogen antagonistic properties. However, during development, the extent to which the bazedoxifene component had estrogen agonist or antagonist properties at other target tissues was not clear.

The Applicant was informed that two studies would be needed to demonstrate endometrial safety, and two-year BMD data would be required along with fracture data to support the prevention of PMO indication. Agreement was reached that the bazedoxifene monotherapy fracture data would be sufficient to support the prevention of osteoporosis indication. The End-of-Phase 2 meeting (July 25, 2001), stressed the importance of defining the lowest effective dose to prevent endometrial hyperplasia. Trial 3115A1-304, designed to be the confirmatory study for endometrial safety and postmenopausal osteoporosis prevention was conducted under a Special Protocol Assessment as was the replacement study Trial 3115A1-3307.

7.1 Dose-finding

Trial 3068A1-203-EU:
Prior to opening the IND, Trial 3068A1-203-EU was initiated in the European Union in June, 1999, and functions as the primary dose-finding study for the conjugated estrogens/ bazedoxifene combination (see pages 32 – 37 of the primary clinical review). The primary objective of this 12-week trial was to explore the effects of the combination of 2 doses (0.3 mg and 0.625 mg) of Premarin with 3 doses (5 mg, 10 mg, and 20 mg) of bazedoxifene on the endometrium as assessed with transvaginal ultrasonography (TVUS) and endometrial biopsies in postmenopausal women. The effects on vasomotor symptoms were also assessed. Premarin and bazedoxifene were administered as separate tablets in this study. Eleven dose groups were utilized in this study including placebo, active control Premarin 0.625/medroxyprogesterone

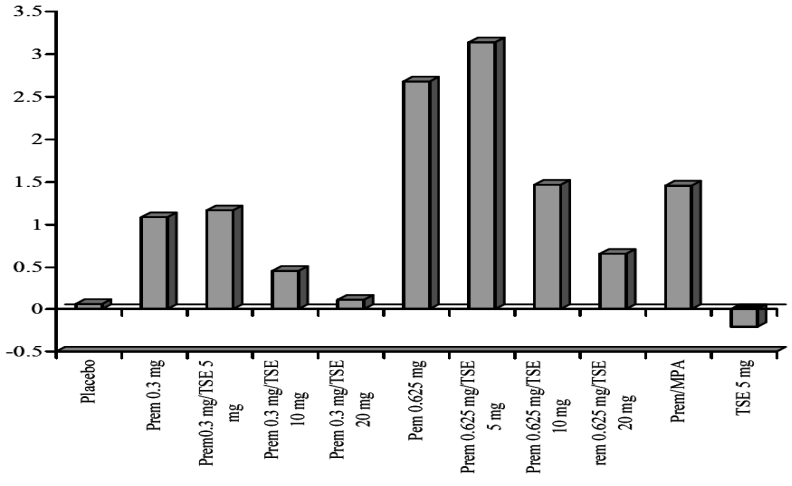
acetate 2.5 mg, Premarin 0.625, Premarin 0.3, Premarin 0.625 + bazedoxifene 5, Premarin 0.625 + bazedoxifene 10, Premarin 0.625 + bazedoxifene 20, Premarin 0.3 + bazedoxifene 5, Premarin 0.3 + bazedoxifene 10, and Premarin 0.3 + bazedoxifene 20. Enrolled subjects were 40-65 years old, 1 to 10 years post menopause with an average of 4 hot flushes a day. A total of 414 subjects were enrolled in the trial and 408 subjects took at least one dose of study medication. Each subject took three active drug or placebo tablets daily to maintain the blinding. The intent-to-treat (ITT) population and per protocol (PP) populations were identical and consisted of 397 subjects who had at least one post-baseline transvaginal ultrasound.

The mean age for each treatment group ranged from 52 – 55 years, with an age range for the study of 41 – 65 years. Enrolled subjects were predominantly Caucasian with time since last menopause raging from 1 – 16 years. Forty-eight percent of the enrolled population had previously used hormone replacement therapy.

Endometrial thickness was read both locally at the site and by a central facility. The central evaluation data were recorded only when there was a discrepancy with the local site reading. The two primary comparison groups were Premarin 0.625/bazedoxifene 20 versus Premarin 0.625 alone; and Premarin 0.3/bazedoxifene 20 versus Premarin 0.3 alone. All other comparisons were considered secondary or exploratory and no adjustment for multiplicity was made.

As shown in Figure 2 below, the 5 mg dose of bazedoxifene was not effective in decreasing the endometrial thickness and the 20 mg bazedoxifene dose achieved significant reductions in endometrial thickness compared to the corresponding Premarin only dose (-0.98 for Premarin 0.3/bazedoxifene 20 versus Premarin 0.3 alone, p=0.049); -1.95 Premarin 0.625/bazedoxifene 20 versus Premarin 0.625 alone, p<0.001).

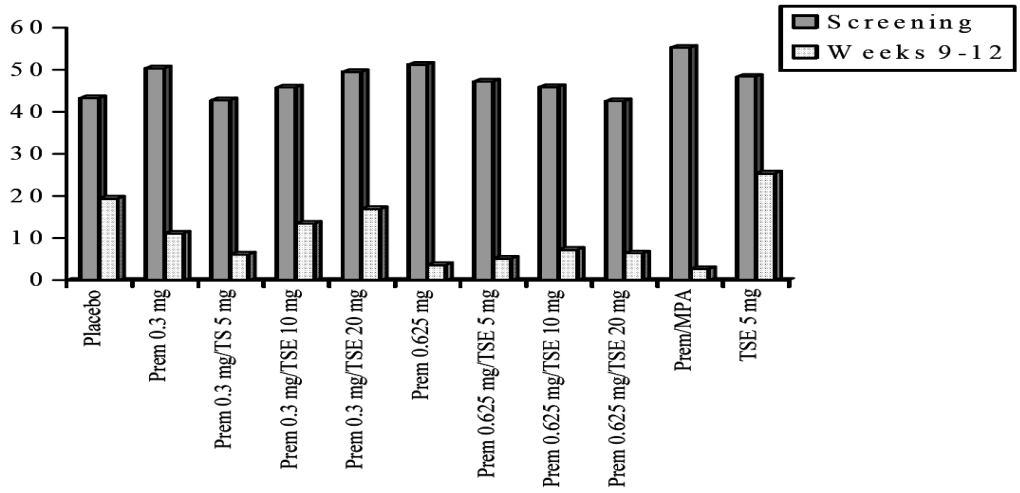
Figure 2: Trial 3068A1-203-EU: Mean Change (mm) from Baseline in Endometrial Thickness, Local Site Evaluation (Source: Figure 9.4.1.1-1, page 65, CSR35419)



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

Subjects recorded the number and severity of hot flushes on diary cards. The average number of hot flushes at baseline was 43 to 55 per week. As displayed in Figure 3 below, treatment with all doses and combinations of estrogen resulted in decreases in the number of hot flushes per week with better results achieved with the 0.625 mg Premarin dose.

Figure 3: Trial 3068A1-203-EU: Absolute Mean Number of Hot Flushes per Week at Screening and Weeks 9 to 12 (Source: Figure 9.4.5.1-1, page 79, CSR35419)



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

Based on the results achieved, the Applicant chose to proceed with evaluation of bazedoxifene combined with 0.625 mg and 0.45 mg conjugated estrogens.

Trial 3115A1-303-US/EU/BR was begun in April, 2002, and played a role in dose-finding, evaluating the effects of the combination of 0.45 mg and 0.625 mg of conjugated estrogens in combination with 10 mg, 20 mg, and 40 mg of bazedoxifene. Effects on the endometrium as assessed with transvaginal ultrasonography and endometrial biopsies were evaluated. Trial 3115A1-303 is also the primary trial supporting the osteoporosis indication and endometrial safety and will be discussed in depth in sections 7.4 and 8.1 of this review.

7.2 Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause

The Applicant is seeking an indication for treatment of moderate to severe vasomotor symptoms associated with menopause. As outlined in the 2003 Draft Guidance *"Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations of Clinical Evaluation"* for the treatment of moderate to severe vasomotor symptoms, symptom severity is defined as: Mild – sensation of heat without sweating; Moderate – sensation of heat with sweating, able to continue activity; and Severe – sensation of heat with sweating, causing cessation of activity. The following co-primary endpoints are recommended:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

The indication for the treatment of moderate to severe vasomotor symptoms associated with menopause is supported by Trial 3115A1-305-US.

Trial 3115A1-305-US

This is a 12 week, randomized, double-blind, placebo-controlled trial in symptomatic postmenopausal women with an intact uterus 40 to 65 years old. Subjects reported at least 7 moderate to severe hot flushes per day or 50 per week and met the criteria for postmenopausal defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea and a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL. Eligible subjects were randomized to 2:2:1 to receive conjugated estrogen 0.625/bazedoxifene 20, conjugated estrogen 0.45/bazedoxifene 20, or placebo. Formulation B was used in this trial. The four prespecified co-primary endpoints of the trial are average daily number of moderate and severe hot flushes at Week 4 and Week 12 compared to placebo and the average daily severity of hot flushes at Week 4 and Week 12 compared to placebo. Responder analyses of subjects who reached at least a 50% or a 75% decrease from baseline in the number of hot flushes were secondary endpoints of the trial.

Population: A total of 332 subjects were randomized, 318 took at least one dose of study drug, and 277 (87%) completed the study (Table 1 below). The primary reasons for discontinuation were protocol violations (14 (4%) subjects) and adverse events (14 (4%) subjects). The overall rate of discontinuations was balanced. However imbalances in discontinuations are noted for discontinuation due to adverse events, occurring in 2-4% in the conjugated estrogens/ bazedoxifene groups compared to 10% in the placebo group and discontinuation due to lost to follow-up, which occurred for 5 subjects in the 0.625/20 group and no subjects in the 0.45/20 or placebo group. The mean age of the study population was 53 years with a range of 42 – 64 years. Enrollees were predominantly of white race and mean body mass index of 26 kg/m^2. The mean number of years since last menstrual period was approximately 4.5 years with a range of 6 months to 19 years.

Table 1: Trial 3115A1- 305: Patient Disposition			
	CE 0.45 / BZA 20	**CE 0.625 / BZA 20**	**Placebo**
N, randomized	133	(b) (4)	66
N, treated	127		63
Discontinued	14 (11)		10 (16)
Adverse Event	5 (4)		6 (10)
Protocol Violation	5 (4)		2 (3)
Lost to Follow-up	0		0
Patient request	3 (2)		1 (1)
Unsatisfactory response	1 (1)		1 (1)
N, safety	127		63
N, mITT	122		63
Completed Study	113 (89)		53 (84)
Source: compiled by reviewer from tables 8-1 and 8-2, CSR67461			

Efficacy: The primary analysis utilized Last Observation Carried Forward (LOCF) for the modified intent-to-treat (mITT) population. The mITT population included 310 (98%) subjects who were randomized, took at least 1 dose of study drug, and recorded at least 5 days of data for the baseline week and at least one on-therapy week. Reduction in the average daily number of moderate to severe hot flushes and severity of moderate to severe hot flushes was compared between the active therapy groups and placebo using an analysis of covariance (ANCOVA) with treatment and study site as factors and baseline values as a covariate. As outlined in Table 2 below, both the conjugated estrogens 0.45/bazedoxifene 20 dose and the conjugated estrogens 0.625/bazedoxifene 20 dose were effective in reducing the average number of moderate to severe hot flushes and severity of daily moderate to severe hot flushes.

A placebo effect is noted for average number of daily moderate to severe hot flushes with placebo-treated subjects reporting a mean decrease of 2.8 moderate to severe hot flushes at Week 4 and a decrease of 4.9 moderate to severe hot flushes at Week 12. The treatment difference for conjugated estrogens 0.45/bazedoxifene 20 is -3.07 at Week 4 and -2.71 at Week 12. For conjugated estrogens 0.625/bazedoxifene 20, the treatment difference was (b) (4) at Week 4 and (b) (4) at Week 12.

For average severity of moderate to severe hot flushes, the mean decrease for placebo treated subjects is -0.09 at Week 4 and -0.26 at Week 12. The treatment difference conjugated estrogens 0.45 /bazedoxifene 20 is -0.58 at Week 4 and -0.87 at Week 12. For conjugated estrogens 0.625 /bazedoxifene 20, the treatment difference was (b) (4) at Week 4 and (b) (4) at Week 12.

Table 2: Trial 3115A1- 305: Changes from Baseline in Average Number and Average Daily Severity of Moderate to Severe Hot Flushes (mITT, LOCF)			
	CE 0.45 / BZA 20 N=127	**CE 0.625 / BZA 20 N=128**	**Placebo N=63**
n, mITT	122	(b) (4)	63
Average Number of Daily Moderate to Severe Hot Flushes			
Baseline, mean (SD)	10.3 (5.4)	(b) (4)	10.5 (5.0)
Week 4			
Mean number (SD)	4.5 (4.6)		7.5 (8.1)
Change from baseline, mean (SE)	-5.9 (0.42)		-2.8 (0.56)
Treatment Difference (95% CI)	-3.07 (-4.40 , -1.73)		
p value vs. placebo	<0.001		
Week 12			
Mean number (SD)	2.8 (3.6)		5.4 (6.0)
Change from baseline, mean (SE)	-7.6 (0.36)		-4.9 (0.48)
Treatment Difference (95% CI)	-2.71 (-3.84 , -1.57)		
p value vs. placebo	<0.001		
Average Severity of Daily Moderate to Severe Hot Flushes			
Baseline, mean (SD)	2.3 (0.31)	(b) (4)	2.3 (0.33)
Week 4			
Mean (SD)	1.7 (0.79)		2.1 (0.56)
Change from baseline, mean (SE)	-0.58 (0.07)		-0.09 (0.09)
Treatment Difference (95% CI)	-0.48 (-0.70 , -0.27)		
p value vs. placebo	<0.001		
Week 12			
Mean (SD)	1.4 (0.91)		1.9 (0.69)
Change from baseline, mean (SE)	-0.87 (0.08)		-0.26 (0.11)
Treatment Difference (95% CI)	-0.60 (-0.86 , -0.35)		
p value vs. placebo	<0.001		
Source: Supportive Tables 15.11 and 15 13 csr 67461, and Tables 5 and 6, page 10 Statistical Review			

Missing Source Documentation: Missing source documentation has plagued the Duavee development program. In study 305, source documentation for five subjects could not be located and results could not be verified. Sensitivity analyses conducted by the Applicant and confirmed by Dr. Dwyer are displayed in Tables 13 and 14, page 18 of the statistical review. The results of the sensitivity analyses were consistent with the primary analyses.

The Office of Scientific Investigations inspected one study site for trial 3115A1-305-US. The preliminary classification for site 538 (Dr. Christopher Hutchinson) is OAI. A sensitivity analysis excluding this site was performed. As outlined in Table 3 below, excluding subjects from site 538 did not significantly change the efficacy results. Should the final classification for site 538 remain OAI, the values reported in the product label should exclude the data from site 538.

Table 3: Trial 3115A1- 305: Changes from Baseline in Average Number and Average Daily Severity of Moderate to Severe Hot Flushes, Excluding Subjects from Study Site 538 (mITT, LOCF)			
	CE 0.45 / BZA 20 N=127	**CE 0.625 / BZA 20 N=** (b) (4)	**Placebo N=63**
n, mITT	122	(b) (4)	63
n, mITT excluding site 538	114		59
Average Number of Daily Moderate to Severe Hot Flushes			
Baseline, mean (SD)	10.37 (5.45)	(b) (4)	10.68 (5.05)
Week 4			
Change from baseline, mean (SE)[1]	-5.76 (0.44)		-2.85 (0.59)
Treatment Difference (95% CI)[2]	-2.91 (-4.31 , -1.51)		
Week 12			
Change from baseline, mean (SE)[1]	-7.62 (0.38)		-4.81 (0.50)
Treatment Difference (95% CI)[2]	-2.82 (-4.02 , -1.61)		
Average Severity of Daily Moderate to Severe Hot Flushes			
Baseline, mean (SD)1	2.33 (0.31)	(b) (4)	2.26 (0.32)
Week 4			
Change from baseline, mean (SE)[1]	-0.54 (0.07)		-0.09 (0.09)
Treatment Difference (95% CI)[2]	-0.45 (-0.67 , -0.23)		
Week 12			
Change from baseline, mean (SE)[1]	-0.85 (0.08)		-0.20 (0.11)
Treatment Difference (95% CI)[2]	-0.65 (-0.92 , -0.39)		

[1]Change from Baseline using raw data
[2] Based on raw data analysis using ANCOVA model Difference = Treatment + Baseline + Site
Source: Analysis by Statistical Reviewer

The responder analyses and other secondary endpoints confirm the primary efficacy findings in that both doses of conjugated estrogens/bazedoxifene were effective in decreasing the average daily number and severity of moderate to severe hot flushes.

Trial 3115A1-303-US/EU/BR

Trial 3115A1-303-US/EU/BR provides supportive evidence of efficacy for Duavee. The trial was begun in April, 2002 and preceded the 2003 draft guidance for vasomotor symptoms. Data on the average number and severity of hot flushes were collected in a small subgroup of subjects (n=217, 13-33 subjects per group). The initial analysis counted only moderate and severe hot flushes for the severity score. However, the Applicant changed the primary analysis so that all hot flushes, including mild ones were counted in the severity score. A stepwise statistical approach was used to address multiplicity.

As outlined in Table 22 on page 59 and Table 23 on page 61 of the clinical review, the mean age of the population in the vasomotor symptoms substudy was 54.7 years and subjects were 6.2 years since last menstrual period. Sixty nine (31%) subjects discontinued the trial with adverse events being the most common reason for discontinuation. Nineteen (57%) subjects in the placebo group discontinued the study with eight subjects withdrawing due to unsatisfactory response.

As outlined in the Table 4 below, both the conjugated estrogens 0.45/bazedoxifene 20 dose and the conjugated estrogens 0.625/bazedoxifene 20 dose were effective in reducing the average number of daily moderate to severe hot flushes at Week 4 and Week 12. For the

average severity of daily hot flushes, both doses of Duavee were only effective at reducing the severity of hot flushes at Week 12.

Table 4: Trial 3115A1- 303: Changes from Baseline in Average Number and Average Daily Severity of Moderate to Sever Hot Flushes (EE1, LOCF)

	CE 0.45 / BZA 20	CE 0.625 / BZA 20	Placebo
n, mITT	28	(b) (4)	33
Average Number of Daily Hot Flushes			
Baseline, mean (SD)	11.4 (4.9)	(b) (4)	14.3 (12.9)
Week 4			
Change from baseline, mean (SE)	-5.5 (1.01)		-1.9 (0.98)
p-value vs. placebo	0.011		
Week 12			
Change from baseline, mean (SE)	-8.5 (1.04)		-2.4 (1.02)
p-value vs. placebo	<0.001		
Average Severity of Daily Hot Flushes			
Baseline, mean (SD)	2.6 (0.32)	(b) (4)	2.5 (0.36)
Week 4			
Change from baseline, mean (SE)	-0.38 (0.13)		-0.09 (0.09)
p-value vs. placebo	0.406		
Week 12			
Change from baseline, mean (SE)	-1.00 (0.15)		-0.26 (0.11)
p-value vs. placebo	<0.001		

Source: Adapted from Tables 29, 30, and 31on pages 66-68, Primary Clinical Review

Efficacy Summary: I agree with the clinical and statistical reviewers that Trial 3115A1-305 demonstrates that both conjugated estrogens 0.45/bazedoxifene 20 and conjugated estrogens 0.625/bazedoxifene 20 are efficacious in reducing the incidence and severity of moderate and severe hot flushes associated with menopause. The placebo-subtracted treatment difference in the mean number of daily moderate to severe hot flushes is -2.9 at Week 4 and -2.8 at Week 12 for the conjugated estrogens 0.45/bazedoxifene 20 dose and (b) (4) at Week 4 and (b) (4) at Week 12 for the conjugated estrogens 0.625/bazedoxifene 20 dose. For average severity score, the placebo-subtracted treatment difference is -0.45 at Week 4 and -0.65 at Week 12 for the conjugated estrogens 0.45/bazedoxifene 20 dose and (b) (4) at Week 4 and (b) (4) at Week 12 for the conjugated estrogens 0.625/bazedoxifene 20 dose. Efficacy is maintained with removal of subjects from study site 538.

7.3 Treatment of Moderate to Severe Vulvar and Vaginal Atrophy Associated with Menopause

(b) (4)

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7.4 Prevention of Postmenopausal Osteoporosis

The Applicant is seeking an indication for prevention of postmenopausal osteoporosis. In general, for all agents except for 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, bazedoxifene 20 mg monotherapy has been shown to be efficacious in reducing the risk of fractures.

Trial 3115A1-303-US/EU/BR is the primary study supporting the prevention of osteoporosis indication. It is also one of the primary studies supporting endometrial safety, discussed in

section 8.1. This trial, begun in April, 2002, is a 24-month, randomized, placebo-and active-controlled trial. A total of 3544 healthy postmenopausal women (age 40-75) with an intact uterus were enrolled in the trial. For this study, postmenopausal is defined as 12 months of spontaneous amenorrhea, a serum follicle-stimulating hormone (FSH) level ≥ 30 mIU/mL, and serum 17β estradiol level ≤ 50 pg/mL. Two osteoporosis substudies were part of the trial. Subjects enrolled in the osteoporosis substudies had bone mineral density (BMD) measurements at baseline. In the Osteoporosis Prevention Substudy I subjects were more than 5 years postmenopausal with a BMD T-score at the lumbar spine or total hip between –1 and –2.5 (inclusive), and at least 1 additional risk factor for osteoporosis. In the Osteoporosis Prevention II Substudy subjects were between 1 year and 5 years postmenopausal and had at least 1 additional risk factor for osteoporosis.

Eligible subjects were randomized into 8 treatment groups to receive conjugated estrogen 0.625mg with bazedoxifene 10 mg, 20mg or 40 mg, conjugated estrogen 0.45 with bazedoxifene 10 mg, 20mg or 40 mg, placebo, or active-control raloxifene 60 mg. This section of the review will focus on the osteoporosis results and the doses that the sponsor is seeking for marketing, conjugated estrogens 0.625/ bazedoxifene 20 and conjugated estrogens 0.45/ bazedoxifene 20. Formulation A was used in this trial. Subjects also received calcium and vitamin D supplementation if dietary intake was inadequate. The primary endpoint of the trial was the incidence of endometrial hyperplasia after 1 year of therapy (results discussed in section 8.1). The main secondary endpoint was the mean percent change from baseline in lumbar spine BMD after 2 years of therapy. Other secondary endpoints included bone mineral density of the lumbar spine, hip and distal radius at other time points including 6 months, 12 months and 24 months. The BMD modified intent-to-treat (mITT) population included all subjects who took at least one dose of study drug and had baseline and at least one on-therapy BMD. Last observation carried forward was used for the analyses. ANCOVA was the main model for analysis and used treatment and center for factors and baseline BMD and years since menopause as covariates. To address multiplicity, a stepwise approach was used beginning with conjugated estrogens 0.625 /bazedoxifene 10, followed by increasing strengths of bazedoxifene (20 mg, then 40 mg) and then the 0.45 dose regimens. The Osteoporosis II group was tested first. All comparisons were 2-sided at the 0.048 level (with adjustment for an interim analysis).

For the Osteoporosis Substudy II, assuming a standard deviation of 3.5 for the mean percent change from baseline in lumbar spine BMD, a sample size of 67 subjects per group would provide 90% power to detect a difference of 2.0% in the mean percent change at the 0.048 level. To account for smaller changes at the hip, the sample size was increased to 100 per group. For the Osteoporosis Substudy I, assuming a standard deviation of 3.5 for the mean percent change from baseline in lumbar spine BMD, 117 subjects per group were needed to provide 90% power to detect a difference of 1.5% at the 0.048 level. A sample size of 160 per group was chosen in order to provide 90% or greater power for both lumbar spine and total hip.

Population: A total of 3544 subjects were randomized into the study and 3397 subjects received at least one dose of study drug (Table 10). In the Osteoporosis substudy I, 1454 subjects were randomized and took at least 1 dose of study drug, and 1295 subjects were included in the mITT population. In Osteoporosis substudy II, 861 subjects were randomized and took at least 1 dose of study drug, and 783 subjects were included in the mITT population. The table below lists the disposition for selected treatment groups. In both osteoporosis substudies, the most common reason for study discontinuation was adverse events or patient withdrawal of consent. Discontinuations were generally balanced among treatment groups. The mean age of the overall study population was 56.5 years with a range of 40 – 75 years. Enrollees were predominantly of white race and mean body mass index of 25.8 kg/m^2. The mean number of years since last menstrual period was 8.1 years. In Osteoporosis substudy I, the mean age was 58.5 years, the mean number of years since last menstrual period was 11.1 years, and the baseline mean lumbar spine T score was -1.47. For Osteoporosis substudy II, the mean age was 52.3 years, the mean number of years since last menstrual period was 3.0 years, and the baseline mean lumbar spine T score was in the normal range at -0.83.

Table 10: Trial 3115A1- 303: Subject Disposition, Selected Treatment Groups

	CE 0.45 / BZA 20	CE 0.625 / BZA 20	Raloxifene 60	Placebo
Osteoporosis Substudy I (> 5 Years Since Menopause)				
N, treated	173	(b) (4)	188	184
Discontinued	51 (28)		53 (28)	64 (35)
Adverse Event	25 (14)		20 (11)	28 (15)
Death	0		0	0
Lost to follow-up	4 (2)		4 (2)	3 (2)
Other	7 (4)		7 (4)	8 (4)
Protocol deviation	0		1 (1)	5 (3)
Patient request/withdrew consent	15 (8)		19 (10)	19 (10)
Lack of efficacy	0		2 (1)	1 (1)
N, safety	173		188	184
N, mITT	160		164	159
N, Completed Study	131 (72)		135 (72)	120 (65)
Osteoporosis Substudy II (≤ 5 years Since Menopause)				
N, treated	111	(b) (4)	107	108
Discontinued	26 (23)		39 (36)	34 (32)
Adverse Event	5 (5)		15 (14)	16 (15)
Death	0		0	0
Lost to follow-up	4 (4)		7 (6)	2 (2)
Other	6 (5)		7 (6)	8 (7)
Protocol deviation	2 (2)		1 (1)	2 (2)
Patient request/withdrew consent	8 (7)		8 (8)	5 (5)
Lack of efficacy	1 (1)		1 (1)	1 (1)
N, safety	111		107	108
N, mITT	101		97	99
N, Completed Study	85 (77)		68 (64)	74 (68)

Source: compiled by reviewer from tables 3.1 and 3.2, Statistical Review

Efficacy Endpoints:

Percent Change in Lumbar Spine BMD at Month 24: Mean percent change from baseline in lumbar spine BMD at Month 24 was a key secondary endpoint for the trial. Analyses were conducted using an ANCOVA model in the mITT population using treatment and center as factors and baseline BMD and years since menopause as covariates. As outlined in Table 11, for subjects more than 5 years post menopause treatment with conjugated estrogens 0.45/bazedoxifene 20 resulted in a 3.1% increase in lumbar spine BMD over placebo at 24 months. Similarly, treatment with conjugated estrogens 0.625/bazedoxifene 20 increased BMD (b) (4) compared to placebo. For subjects 5 years or less post menopause the placebo subtracted treatment difference at 24 months was 3.6% for conjugated estrogens 0.45/bazedoxifene 20 and (b) (4) for conjugated estrogens 0.625/bazedoxifene 20.

Table 11: Trial 3115A1- 303: Percent Change in Lumbar Spine BMD at 24 Months, Selected Treatment Groups (mITT, LOCF)

	CE 0.45 / BZA 20	CE 0.625 / BZA 20	Raloxifene 60	Placebo
Osteoporosis Substudy I (> 5 Years Since Menopause)				
N, treated	173	(b) (4)	188	184
N, mITT	160		164	159
LS Mean Change (%)	1.57		0.72	-1.51
Treatment Difference vs. placebo	3.08		2.23	
95% CI	2.26 , 3.89		1.42 , 3.04	
p-value	< 0.001		< 0.001	
Osteoporosis Substudy II (≤ 5 years Since Menopause)				
N, treated	111	(b) (4)	107	108
N, mITT	101		97	99
LS Mean Change	1.69		0.15	-1.92
Treatment Difference vs. placebo	3.61		2.07	
95% CI	2.64 , 4.57		1.09 , 3.05	
p-value	< 0.001		< 0.001	
Source: compiled by reviewer from table 3.3, Statistical Review				

Percent Change in Total Hip BMD at Month 24: Mean percent change from baseline in total hip BMD at Month 24 was a secondary endpoint for the trial and represents an important evaluation for labeling. As outlined in Table 12, for subjects more than 5 years post menopause, the placebo subtracted treatment difference at 24 months in total hip BMD was 1.7% for conjugated estrogens 0.45/bazedoxifene 20 and (b) (4) for conjugated estrogens 0.625/bazedoxifene 20. For subjects 5 years or less post menopause, the placebo subtracted treatment difference at 24 months was 1.9% for conjugated estrogens 0.45/bazedoxifene 20 and (b) (4) for conjugated estrogens 0.625/bazedoxifene 20.

Table 12: Trial 3115A1- 303: Percent Change in Total Hip BMD at 24 Months, Selected Treatment Groups (mITT, LOCF)				
	CE 0.45 / BZA 20	**CE 0.625 / BZA 20**	**Raloxifene 60**	**Placebo**
Osteoporosis Substudy I (> 5 Years Since Menopause)				
N, treated	173	(b) (4)	188	184
N, mITT	160		164	158
LS Mean Change (%)	1.06		0.88	-0.65
Treatment Difference vs. placebo	1.71		1.53	
95% CI	1.16 , 2.26		0.98 , 2.08	
p-value	< 0.001		< 0.001	
Osteoporosis Substudy II (≤ 5 years Since Menopause)				
N, treated	111	(b) (4)	107	108
N, mITT	102		96	99
LS Mean Change	0.46		-0.27	-1.41
Treatment Difference vs. placebo	1.87		1.14	
95% CI	1.19 , 2.54		0.45 , 1.82	
p-value	< 0.001		0.011	
Source: compiled by reviewer from table 3.5, Statistical Review				

Missing Source Documentation: In trial 3115A1-303, source documentation was missing for 8% of subjects overall (17 (8%) in the conjugated estrogens 0.45/ bazedoxifene 20 group, (b) (4) (b) (4) in the conjugated estrogens 0.625/ bazedoxifene 20 group, 7 (7%) in the placebo group, and 9 (8%) in the bazedoxifene group). Because results could not be verified, sensitivity analyses excluding these subjects were conducted.

As outlined in Table 13, after excluding patients with missing source documentation, the treatment difference in lumbar spine BMD in Osteoporosis substudy I subjects remained stable at 3.1% for the conjugated estrogens 0.45/ bazedoxifene 20 group and (b) (4) (b) (4) for the conjugated estrogens 0.625/ bazedoxifene 20 group. For osteoporosis substudy II subjects, the treatment difference remained 3.6% for the conjugated estrogens 0.45/ bazedoxifene 20 group and (b) (4) for the conjugated estrogens 0.625/ bazedoxifene 20 group.

For the total hip, the treatment difference at Month 24 for substudy I subjects remained 1.7% for the conjugated estrogens 0.45/ bazedoxifene 20 group and (b) (4) for the conjugated estrogens 0.625/ bazedoxifene 20 group. In substudy 2, the treatment difference for the conjugated estrogens 0.45/ bazedoxifene 20 group increased from 1.9% to 2.0%. For the conjugated estrogens 0.625/ bazedoxifene 20 group, the treatment difference (b) (4) (b) (4) with exclusion of subjects with missing source documentation.

In all cases, these are small changes that do not change the clinical outcomes of the trial.

Table 13: Trial 3115A1- 303: Percent Change in Lumbar Spine and Total Hip BMD at 24 Months, Excluding Subjects with Missing Source Documentation, Selected Treatment Groups (mITT, LOCF)				
	CE 0.45 / BZA 20	**CE 0.625 / BZA 20**	**Raloxifene 60**	**Placebo**
Change in Lumbar Spine BMD, Osteoporosis Substudy I (> 5 Years Since Menopause)				
N, treated	173	(b) (4)	188	184
N, original mITT	160		164	159
N, revised mITT	155		157	151
LS Mean Change (%)	1.64		0.75	-1.47
Treatment Difference vs. placebo	3.11		2.22	
95% CI	2.29 , 3.93		1.40 , 3.04	
p-value	< 0.001		< 0.001	
Change in Lumbar Spine BMD, Osteoporosis Substudy II (≤ 5 years Since Menopause)				
N, treated	111	(b) (4)	107	108
N, original mITT	101		97	99
N, revised mITT	95		90	95
LS Mean Change	1.72		0.13	-1.90
Treatment Difference vs. placebo	3.62		2.03	
95% CI	2.64 , 4.60		1.03 , 3.02	
p-value	< 0.001		< 0.001	
Change in Total Hip BMD, Osteoporosis Substudy I (> 5 Years Since Menopause)				
N, treated	173	(b) (4)	188	184
N, original mITT	160		164	158
N, revised mITT	155		157	150
LS Mean Change (%)	1.07		0.87	-0.65
Treatment Difference vs. placebo	1.73		1.53	
95% CI	1.17 , 2.28		0.97 , 2.08	
p-value	< 0.001		< 0.001	
Change in Total Hip BMD, Osteoporosis Substudy II (≤ 5 years Since Menopause)				
N, treated	111	(b) (4)	107	108
N, original mITT	102		96	99
N, revised mITT	96		89	95
LS Mean Change	0.55		-0.31	-1.42
Treatment Difference vs. placebo	1.96		1.10	
95% CI	1.28 , 2.65		0.40 , 1.80	
p-value	< 0.001		0.011	
Source: compiled by reviewer from tables 3.4 and 3.6, Statistical Review				

Trial 3115A1-3307-WW:

Trial 3115A1-3307-WW, begun in 2009, is a 1-year, double-blind, randomized, placebo and active controlled study that was conducted as a replacement for trial 3115A1-304-WW. Trial 3115A1-304-WW utilized Formulations B and C and (b) (4) further discussed in section 8.1 below. The bazedoxifene exposure of Formulation C was found to be 16 – 32% less than that of Formulation A and this was postulated to be the reason for the high rate of endometrial hyperplasia. Therefore, Trial 3115A1-3307-WW functions as the second trial for demonstration of endometrial safety and also as a confirmatory trial for the osteoporosis prevention indication. Trial 3115A1-3307-WW was conducted under a Special Protocol Assessment and agreements were reached regarding support for endometrial protection and the osteoporosis prevention indication.

A total of 1886 healthy postmenopausal women age 40 to 65 years with an intact uterus were randomized into five dose groups: conjugated estrogens 0.625/bazedoxifene 20, conjugated estrogens 0.45/bazedoxifene 20, bazedoxifene 20, conjugated estrogens 0.45/medroxyprogesterone acetate 1.5, or placebo. The primary endpoint is endometrial safety at 1 year. Substudies included an osteoporosis substudy, a breast density substudy, and a sleep substudy. For the osteoporosis substudy, enrolled subjects were within 5 years of menopause. The key osteoporosis endpoint was change in lumbar spine bone mineral density at 12 months.

Population: A total of 602 subjects were randomized into the Osteoporosis Substudy, 590 subjects received at least one dose of study drug, 512 subjects are included in the mITT analysis, and 475 subjects (80%) completed the trial. In the Osteoporosis substudy, the mean age was 53 years with an age range of 42 to 63 years, the mean BMI was 25.8 kg/m^2, the mean number of years since last menstrual period was 2.5 years, and the baseline mean lumbar spine T score was in the normal range at -0.90.

Table 14: Trial 3115A1- 3307: Subject Disposition, Osteoporosis Substudy

	CE 0.45 / BZA 20	CE 0.625 / BZA 20	BZA 20	CE 0.45 / MPA 1.5	Placebo
N, treated	135	(b) (4)	73	70	158
Discontinued	26 (19)		18 (25)	19 (27)	29 (18)
Adverse Event	10 (7)		7 (10)	8 (11)	9 (6)
Investigator request	0		0	0	0
Lost to follow-up	1 (1)		3 (4)	3 (4)	0
Other	3 (2)		2 (3)	0	6 (4)
Protocol violation	2 (2)		2 (3)	4 (6)	4 (2)
Patient request/withdrew consent	9 (7)		0	2 (3)	7 (4)
Lack of efficacy	1 (1)		4 (6)	2 (3)	3 (2)
N, safety	135		73	70	158
N, mITT	119		56	59	139
N, Completed Study	109 (81)		55 (75)	51 (73)	129 (82)

Source: compiled by reviewer from tables 8-1 and 8-3, csr 81040

Efficacy Endpoints:
Percent Change in Lumbar Spine BMD at Month 12: Mean percent change from baseline in lumbar spine BMD at Month 12 was a key secondary endpoint for Trial 3115A1-3307. Analyses were conducted using an ANCOVA model in the mITT population using treatment and region as factors and baseline BMD and years since menopause as covariates. As outlined in Table 15, at 12 months, the placebo subtracted treatment difference in lumbar spine BMD was 1.5% for the conjugated estrogens 0.45/bazedoxifene 20 group and (b) (4) conjugated estrogens 0.625/bazedoxifene 20 group.

Table 15: Trial 3115A1- 3307: Percent Change in Lumbar Spine BMD at Month 12 (mITT, LOCF)					
	CE 0.45 / BZA 20	CE 0.625 / BZA 20	BZA 20	CE 0.45 / MPA 1.5	Placebo
N, treated	135	(b) (4)	73	70	158
N, mITT	119		56	59	139
LS Mean Change (%)	0.24		0.07	1.30	-1.28
Treatment Difference	1.51		1.34	2.57	
95% CI	0.82 , 2.20		0.47 , 2.21	1.72 , 3.43	
p-value	<0.001		0.0026	<0.001	
Source: compiled by reviewer from table 3.8, Statistical Review					

Percent Change in Total Hip BMD at Month 12: Mean percent change from baseline in total hip BMD at Month 12 was a secondary endpoint for Trial 3115A1-3307. As outlined in Table 16, the placebo subtracted treatment difference in total hip BMD at 12 months is 1.2% for the conjugated estrogens 0.45/bazedoxifene 20 group and (b) (4) for the conjugated estrogens 0.625/bazedoxifene 20 group.

Table 16: Trial 3115A1- 3307: Percent Change in Total BMD at Month 12 (mITT, LOCF)					
	CE 0.45 / BZA 20	CE 0.625 / BZA 20	BZA 20	CE 0.45 / MPA 1.5	Placebo
N, treated	135	(b) (4)	73	70	158
N, mITT	119		56	59	139
LS Mean Change (%)	0.50		0.47	0.71	-0.72
Treatment Difference	1.21		1.19	1.42	
95% CI	0.76 , 1.67		0.61 , 1.77	0.85 , 1.99	
p-value	<0.001		<0.001	<0.001	
Source: compiled by reviewer from table 3.9, Statistical Review					

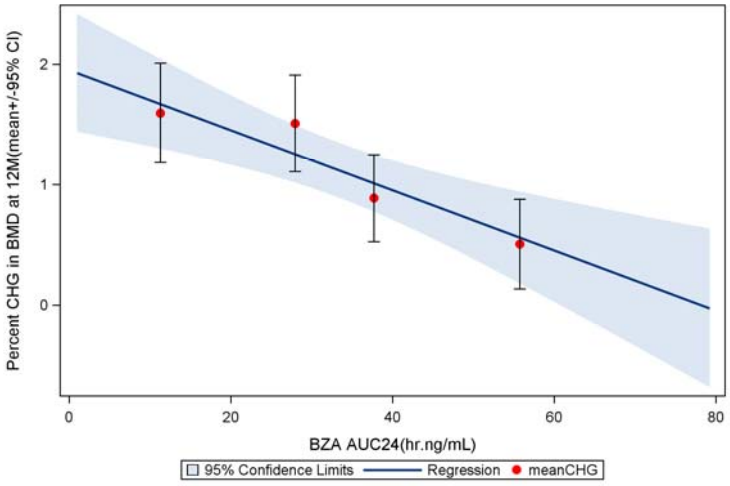
Missing Source Documentation: There are no incidences of missing source documentation in this study.

Efficacy Summary: I agree with the clinical and statistical reviewers that treatment with conjugated estrogens 0.45/bazedoxifene 20 and conjugated estrogens 0.625/bazedoxifene 20 is efficacious in increasing bone mineral density in postmenopausal women. In postmenopausal women less than 5 years post menopause, there was no evidence of a dose response at the lumbar spine. Duavee 0.45/20 increased BMD 3.6% and Duavee 0.625/20 (b) (4) at Month 24. At the total hip, increases were 2% for Duavee 0.45/20 and (b) (4) for Duavee 0.625/20. In postmenopausal women more than 5 years post menopause, Duavee 0.45/20 increased BMD at the lumbar spine 3.1% and Duavee 0.625/20 (b) (4) at Month 24. At the total hip, increases were 1.7% for Duavee 0.45/20 and (b) (4) for Duavee 0.625/20.

Based on the study results and analyses performed by the pharmacometrics team, the predominant effect on bone mineral density is from the conjugated estrogen component (Figure 4). The addition of bazedoxifene appears to diminish the BMD increases achieved.

The lumbar spine BMD increases achieved appear similar to those achieved with 0.3 mg Premarin in the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study at Month 24 (placebo -2.4%, 0.3 mg Premarin +1.1%).

Figure 4: Trials 3115A1-303 and 3115A1-304: Bazedoxifene Exposure Response Relationship for BMD Changes with Conjugated Estrogens 0.625 mg at Month 12
Source: Clinical Pharmacology slides from Mid Cycle meeting



8. Safety

Important safety signals associated with estrogen products include gynecologic safety, breast cancer risk, cardiovascular safety, cerebrovascular safety and venous thrombotic events. The effects of long term unopposed estrogen therapy on the endometrium are well documented. The effects of estrogen agonist/antagonist products on the endometrium are varied with some products showing more endometrial stimulation than others. Similarly, the impact of estrogen agonist/antagonist therapy on breast cancer risk is varied and dependent on the specific agent. Despite positive effects on lipid metabolism, the Women's Health Initiative (WHI) study demonstrated a lack of cardiac protection with estrogen use[2]. Results from the Raloxifene Use in The Heart (RUTH) study also demonstrated a lack of cardiac protection for this estrogen agonist/antagonist[3]. Cerebrovascular accidents have been associated with estrogen and the estrogen agonist/antagonist tamoxifen[4,5]. While the overall incidence of stroke was not increased with raloxifene use in the RUTH trial, there was a concerning finding of increased risk of death from ischemic stroke with raloxifene use, when compared to placebo. Venous thrombotic events are well known to occur with estrogen products including oral

[2] The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. JAMA. 2004; 291: 1701-1712.
[3] Barrett-Connor E et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006 Jul 13; 355(2):125-37.
[4] Brass LM. Hormone Replacement Therapy and Stroke. *Stroke*. 2004; 35 [Suppl I]:2644-2647.
[5] Bushnell CD and Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology*. 2004 Oct 12; 63(7):1230-3.

contraceptives. Studies with various selective estrogen receptor modulators have shown similar increases in venous thrombotic events.

The purpose of bazedoxifene in this combination tablet is to replace a progestin for the purposes of endometrial protection. In addition to the overall safety profile of the combination product, this review focuses on the endometrial safety provided by bazedoxifene and the known safety concerns with estrogen and estrogen agonist/antagonist products including safety concerns from the bazedoxifene monotherapy program.

8.1 Endometrial Safety

In this combination tablet, the estrogen agonist/antagonist bazedoxifene functions as an estrogen antagonist at the uterus and is intended to provide endometrial protection in lieu of a progestational agent. During product development, the Applicant was informed that two studies would be needed to demonstrate endometrial safety. The 2003 Draft Guidance *"Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations of Clinical Evaluation"* recommends that endometrial biopsies, not uterine ultrasounds be used for the evaluation of endometrial hyperplasia. The biopsies should be obtained at screening, during the conduct of the study, and at end of study; the biopsies should be processed in the same manner by a central laboratory; and three blinded independent expert pathologists should determine the diagnosis of the biopsy slides. The primary endpoint should be incidence rate of endometrial hyperplasia at 12 months. The results from the clinical trial should demonstrate a hyperplasia rate that is ≤ 1% with an upper bound of the one-sided 95 percent confidence interval that does not exceed 4%.

The trials originally intended for support of endometrial safety were Trial 3115A1-303-US/EU/BR and Trial 3115A1-304-WW. The results of Trial 3115A1-304-WW, conducted under a Special Protocol Assessment, revealed surprising findings of a high rate of endometrial hyperplasia. Subsequently, it was discovered that one of the two formulations used in the trial, Formulation C, was not bioequivalent to the original Formulation A and achieved a bazedoxifene exposure that was 16 – 32% less than that of Formulation A. Trial 3115A1-3307-WW, begun in 2009, was conducted as a replacement for trial 3115A1-304-WW for demonstration of endometrial safety. All three endometrial safety trials will be included in this discussion. For a detailed review of the endometrial findings, please see the primary clinical review pages 115 – 158. The initial trial, 3115A1-303-US/EU/BR, preceded the 2003 draft guidance and the Applicant chose to use the same hyperplasia classification system for all three studies. As discussed on page 118 on the primary clinical review, the minor differences in histologic classification should not impact review of the data. All endometrial biopsies were read by two, not three, independent blinded pathologists. If the two pathologists disagreed on the presence of hyperplasia, a third pathologist was consulted and the final determination was by majority.

Trial 3115A1-303-US/EU/BR:
Trial 3115A1-303-US/EU/BR is a 24-month, randomized, placebo-and active-controlled trial. A total of 3544 healthy postmenopausal women (age 40-75) with an intact uterus were enrolled in the trial. Eligible subjects were randomized into 8 treatment groups to receive

conjugated estrogen 0.625mg with bazedoxifene 10 mg, 20mg or 40 mg; conjugated estrogen 0.45 with bazedoxifene 10 mg, 20mg or 40 mg; placebo, or active-control raloxifene 60 mg. Formulation A was used in this trial. Subjects also received calcium and vitamin D supplementation if dietary intake was inadequate. The primary endpoint of the trial was the incidence of endometrial hyperplasia after 1 year of therapy.

The Efficacy Evaluable population was used for analyses of the incidence of endometrial hyperplasia. The EE population included subjects who were randomized, had a screening endometrial biopsy read by at least 2 pathologists, took at least one dose of study drug, had no major protocol violations, had not received other prohibited hormonal medications, and had an on-treatment Month 12 biopsy within 30 days of the last dose of study drug. A total of 2539 subjects (72%) comprised the efficacy evaluable population (320 in the conjugated estrogens 0.45/bazedoxifene 10 group, 335 in the conjugated estrogens 0.45/bazedoxifene 20 group, (b) (4) in the conjugated estrogens 0.45/bazedoxifene 40 group, (b) (4) in the conjugated estrogens 0.625/bazedoxifene 10 group, (b) (4) in the conjugated estrogens 0.625/bazedoxifene 20 group, (b) (4) in the conjugated estrogens 0.625/bazedoxifene 40 group, 298 in the raloxifene 60 group, and 312 in the placebo group).

Disordered proliferative endometrium: As outlined in Table 75, pages 124 – 127 of the primary clinical review, disordered proliferative endometrium occurred in 47 subjects (16 in the conjugated estrogens 0.45/bazedoxifene 10 group, 2 in the conjugated estrogens 0.45/bazedoxifene 20 group, (b) (4) in the conjugated estrogens 0.625/bazedoxifene 10 group and (b) (4) the conjugated estrogens 0.625/bazedoxifene 20 group). Disordered proliferative endometrium is seen as a consequence of estrogen stimulation. All subjects with disordered proliferative endometrium were receiving estrogen and most received the lowest dose of bazedoxifene, 10mg.

Endometrial hyperplasia: As outlined in Table 17, there were no cases of confirmed endometrial hyperplasia in the conjugated estrogens 0.45/bazedoxifene 40 group, the conjugated estrogens 0.625/bazedoxifene 40 group, the raloxifene group, or the placebo group at Month 12 or Month 24. Endometrial hyperplasia was confirmed in 17 subjects by Month 12 and 32 subjects by Month 24. The incidence rates are below 1% with an upper bound of the 95% confidence interval below 4% in all groups except the (b) (4) conjugated estrogens 0.45/bazedoxifene 10 group at Month 24.

Table 17: Trial 3115A1- 303: Subjects with Endometrial Malignancy or Endometrial Hyperplasia Confirmed by Two Pathologists (FDA Analysis, Efficacy Evaluable Population)								
	Month 12				Month 24			
	N	n	Rate (%)	95% CI UL	N	n	Rate (%)	95% CI UL
CE 0.45 / BZA 10	320	3	0.94	2.41	277	7	2.53	4.69
CE 0.45 / BZA 20	335	0	0.00	0.89	293	2	0.68	UL < 4%
CE 0.45 / BZA 40	309	0	0.00	0.96	268	0	0.00	1.11
(b) (4)								
Raloxifene 60	298	0	0.00	1.00	261	0	0.00	1.40
Placebo	312	0	0.00	0.96	259	0	0.00	1.41
Source: compiled by reviewer from tables 78-81, Primary Clinical Review								

Transvaginal Ultrasound: Transvaginal ultrasonography (TVU) was performed at screening, Month 12 and Month 24 at approximately one-third of study sites. Mean change from baseline was reported at both time points. As outlined in Table 18, there is a bazedoxifene dose dependent response for endometrial thickness. The products containing 10 mg bazedoxifene are associated with increased endometrial thickness at both 12 and 24 months when compared to placebo.

Table 18: Trial 3115A1-303: TVU – Mean Change From Baseline in Endometrial Thickness								
	CE0.625/ BZA 10	CE0.625/ BZA 20	CE0.625/ BZA 40	CE0.45/ BZA 10	CE0.45/ BZA 20	CE0.45/ BZA 40	ralox	plac
(b) (4)				N=430	N=433	N=423	N=423	N=427
Month 12								
N, pairs	(b) (4)			117	119	112	109	104
Mean (mm)				1.23	0.50	0.34	0.37	0.37
SE				0.20	0.20	0.20	0.21	0.21
Month 24								
N, pairs	(b) (4)			100	110	100	95	85
Mean (mm)				1.91	0.56	0.03	0.16	0.02
SE				0.24	0.23	0.24	0.25	0.26
Source: CSR 64104, table 10-46								

TVU findings were also evaluated categorically and are summarized in the table below using the following reference criteria

- endometrial thickness
  - absolute value > 5mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

There is evidence of a bazedoxifene dose dependent response for endometrial thickness. The products containing 10 mg bazedoxifene were associated with an increased number of subjects with absolute values of endometrial thickness above 5 mm and 8 mm and increases from baseline greater than 3 mm and 5 mm (Table 19).

Table 19: Trial 3115A1-303: TVU – Subjects with Abnormal TVU								
	0.625/ BZA 10	**0.625/ BZA 20**	**0.625/ BZA 40**	**0.45/ BZA 10** N=430	**0.45/ BZA 20** N=433	**0.45/ BZA 40** N=423	**ralox** N=423	**plac** N=427
Subjects with scans, N	[redacted] (b) (4)			127	128	119	118	114
Endometrial thickness								
value > 5mm				36 (28)	18 (14)	8 (7)	14 (12)	9 (8)
value > 8mm				18 (14)	5 (4)	0	2 (2)	4 (4)
increase > 3mm				28 (22)	15 (12)	6 (5)	5 (4)	5 (4)
increase > 5mm				15 (12)	7 (6)	1 (1)	1 (1)	4 (4)
Ovarian volume increase ≥ 2 cm^3				10 (10)	11 (11)	9 (9)	14 (15)	7 (8)
Ovarian cysts				16 (15)	11 (11)	9 (9)	8 (8)	14 (14)
Source: CSR 64104, tables 10-47, 10-48, 15-126								

Trial 3115A1-3307-WW:
Trial 3115A1-3307-WW is a 1-year, double-blind, randomized, placebo and active controlled study. A total of 1886 healthy postmenopausal women age 40 to 65 years with an intact uterus were randomized into five dose groups: conjugated estrogens 0.625/bazedoxifene 20, conjugated estrogens 0.45/bazedoxifene 20, bazedoxifene 20, conjugated estrogens 0.45/medroxyprogesterone acetate 1.5, or placebo. The primary endpoints are endometrial safety at 1 year.

The Efficacy Evaluable population was used for analyses of the incidence of endometrial hyperplasia. The EE population was comprised of subjects who were randomized, had a screening endometrial biopsy read by at least 2 pathologists, took at least one dose of study drug, had no major protocol violations, had not received other prohibited hormonal medications, and had an on-treatment Month 12 biopsy within 30 days of the last dose of study drug. A total of 1375 subjects (73%) comprised the efficacy evaluable population (335 in the conjugated estrogens 0.45/bazedoxifene 20 group, (b) (4) in the conjugated estrogens 0.625/bazedoxifene 20 group, 169 in the bazedoxifene 20 group, 149 in the conjugated estrogens 0.45/medroxyprogesterone acetate 1.5 group, and 354 in the placebo group).

Disordered proliferative endometrium: Disordered proliferative endometrium was diagnosed by at least one pathologist in 14 subjects (2 in the conjugated estrogens 0.45/bazedoxifene 20 group, (b) (4) the conjugated estrogens 0.625/bazedoxifene 20 group, none in the bazedoxifene 20 group, 2 in the conjugated estrogens 0.45/medroxyprogesterone acetate 1.5 group, and 3 in the placebo group).

Endometrial hyperplasia: Endometrial hyperplasia at Month 12, confirmed by two pathologists, was reported in one subject each in the conjugated estrogens 0.45/bazedoxifene 20 group, [redacted] (b) (4) and the placebo group (Table 20). The incidences were all below 1% with the upper bound of the 95% confidence intervals below 4%.

Table 20: Trial 3115A1- 3307: Subjects with Confirmed Endometrial Hyperplasia as Month 12, FDA Analysis, Efficacy Evaluable Population					
	CE 0.45 / BZA 20	**CE 0.625 / BZA 20**	**BZA 20**	**CE 0.45 / MPA 1.5**	**Placebo**
N, EE	335	(b) (4)	169	149	354
n	1		0	0	1
Incidence (%)	0.30		0.00	0.00	0.28
95% CI UL	1.41		1.76	1.99	1.33
Source: compiled by reviewer from Table 100, Primary Clinical Review					

Transvaginal Ultrasound: Transvaginal ultrasonography was performed at screening, Month 12 and Month 24. Scans were read locally. Criteria for determining scans of potential clinical importance were the following:

- endometrial thickness
  - absolute value > 4mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

A total of 1588 subjects, or 86% of the safety population, were evaluated by TVU (see table below). One or more of the above criteria for potential clinical importance were met by 23% of subjects overall (Table 21). Positive endometrial criteria, particularly absolute thickness >8 mm, were most common in subjects assigned to CE/MPA (17%) and CE.625/BZA (b) (4)), compared to CE.45/BZA (12%), placebo (11%), and BZA 20 mg (8%). Increases in ovarian volume were similar between CE/BZA groups and placebo; detection of ovarian cysts was slightly more frequent with placebo.

Records of subjects with these "potential clinically important" findings were reviewed (blinded to treatment) by the medical monitor to identify those with "clinically important" findings. As shown in the table, clinically important endometrial thickness > 8 mm was determined in 19 subjects overall and was more frequent in (b) (4) CE/MPA subjects. Clinically important ovarian cysts > 20 mm were present in 14 subjects overall and were fairly balanced between treatment groups. There were no subjects determined to have clinically important changes in ovarian volume.

Table 21: Trial 3115A1- 3307: Subjects with Abnormal TVU findings					
	CE 0.45mg BZA 20 mg N=445	**CE 0.625mg BZA 20 mg** (b) (4)	**BZA 20 mg** N=230	**CE 0.45 mg MPA 1.5mg** N=220	**Placebo** N=474
Subjects with scans, N	385		195	182	408
Subjects with Potentially Clinically Important Findings					
Total with abnormalities	77 (20)	(b) (4)	40 (21)	51 (28)	88 (22)
Endometrial thickness, all	45 (12)		16 (8)	31 (17)	46 (11)
absolute value > 4mm	44 (12)		16 (8)	31 (17)	45 (11)
absolute value > 8mm	3 (<1)		0 (0)	4 (2)	2 (<1)
increase from baseline > 3mm	10 (3)		3 (2)	9 (5)	12 (3)
increase from baseline > 5mm	4 (1)		0 (0)	5 (3)	2 (<1)
Ovarian volume increase from baseline ≥ 2 cm^3	23 (8)		17 (12)	13 (9)	25 (8)
Ovarian cyst visualized	21 (7)		18 (12)	15 (11)	39 (12)
Subjects with Clinically Important Findings					
Endometrial Thickness >8mm	3 (0.8)	(b) (4)	0	5 (2.8)	2 (0.5)
Ovarian Cyst >20mm	2 (0.4)		4 (1.7)	1 (0.5)	2 (0.4)
Source: CSR Tables 10-33, 10-34, 10-36					

Trial 3115A1-304-WW:
Trial 3115A1-304-WW is a 1-year, double-blind, randomized, placebo and active controlled study with a 1 year extension. A total of 1061 healthy postmenopausal women age 40 to 65 years with an intact uterus were enrolled into the first year of the trial and randomized into four dose groups: conjugated estrogens 0.45/bazedoxifene 20, conjugated estrogens 0.625/bazedoxifene 20, conjugated estrogens 0.45/medroxyprogesterone acetate 1.5, or placebo. Of the subjects that completed Year 1 of the study, 523 enrolled in Year 2 and remained in the same treatment group. The primary endpoint was endometrial safety at Year 1.

Disordered proliferative endometrium: Disordered proliferative endometrium was diagnosed in 13 subjects, 3 in the conjugated estrogens 0.45/bazedoxifene 20 group and (b) (4) in the conjugated estrogens 0.625/bazedoxifene 20 group.

Endometrial hyperplasia: The first primary efficacy outcome was the incidence of endometrial hyperplasia in the efficacy evaluable population at Month 12. The EE population included subjects who were randomized, had a screening endometrial biopsy read by at least 2 pathologists, took at least one dose of study drug, had no major protocol violations, had not received other prohibited hormonal medications, and had an on-treatment Month 12 biopsy within 30 days of the last dose of study drug. An evaluation was also conducted at Month 24 for the extension study (Table 22). Biopsy samples were read as endometrial hyperplasia by at least one pathologist for 16 subjects (2 in the conjugated estrogens 0.45/bazedoxifene 20 group, (b) (4) the conjugated estrogens 0.625/bazedoxifene 20 group, 2 in the conjugated estrogens 0.45/medroxyprogesterone acetate 1.5 group, and none in the placebo group). For the study endpoint, the reading of endometrial hyperplasia was based on agreement of two

pathologists' reading of the endometrial biopsy samples. At Months 12 and 24, no cases of endometrial hyperplasia were diagnosed for subjects in the conjugated estrogens 0.45 /bazedoxifene 20 group, the conjugated estrogens 0.45/medroxyprogesterone acetate 1.5 group, or the placebo group. For the conjugated estrogens/0.625/bazedoxifene 20 group, the incidence of endometrial hyperplasia was (b) (4) at Month 12 and (b) (4) at Month 24.

Table 22: Trial 3115A1-304-WW: Subjects with Confirmed Endometrial Hyperplasia, FDA Analysis, Efficacy Evaluable Population

Test	BZA 20 / CE0.45 N=361	BZA 20/ CE 0.625 (b) (4)	CE0.45/ MPA 1.5 N=179	Placebo N=172
Month 12				
N	261	(b) (4)	119	135
n (%)	0		0	0
95% CI, upper limit	1.14		2.49	2.19
Month 24				
N	131	(b) (4)	66	79
n (%)	0		0	0
95% CI, upper limit	2.26		4.44	3.72
Source: Tables 93 and 94, Primary Clinical Review				

Because of the reported difference in bioavailability of Formulation B and Formulation C, a review was conducted to evaluate the duration of each formulation used. All subjects began the trial on Formulation B, with an average number of days on Formulation B of 207 days and a range of 7 days to 367 days. During the second year of the trial, all subjects received Formulation C, which was noted to have an 18% lower bioavailability of bazedoxifene, raising a question regarding loss of endometrial protection with the lower bazedoxifene exposure in Formulation C. Of the nine cases of endometrial hyperplasia identified, four cases were identified at the Year 1 biopsy, and the rest at the Year 2 biopsy. All cases of endometrial hyperplasia occurred in the CE .625/BZA 20 group. All subjects began the trial on Formulation B and were switched to Formulation C around 180 days, sometimes later. During Year 2, all subjects received Formulation C. As outlined in Table 23, all endometrial hyperplasia cases occurred when the subjects were on Formulation C. The least number of days on Formulation C before the concerning biopsy was 156 days, with a range of 156 - 557 days.

Table 23: Trial 3115A1-304-WW: Formulation Exposure in Subjects with Endometrial Hyperplasia					
Subject Id	**Form B stop**	**Form C start**	**Form C stop**	**Days on Form C to Bx**	**Study Day of Bx**
[redacted] (b) (4)					

Transvaginal Ultrasound: Transvaginal ultrasonography was performed at screening, Month 12 and Month 24. Scans were read locally. Determination of scans with potential clinical importance was done using the following reference criteria:

- endometrial thickness
  - absolute value > 4mm; absolute value > 8mm
  - increase from baseline > 3mm; increase from baseline > 5mm
- ovarian volume – increase from baseline ≥ 2 cm^3
- ovarian cysts – any cyst (either right or left ovary)

A total of 854 (80%) subjects enrolled in the study had transvaginal ultrasonography performed (Table 24). Two hundred and ninety subjects were identified with potentially clinically important TVU scans (90 (30%) in the conjugated estrogens 0.45/bazedoxifene 20 group, [redacted] (b) (4) in the conjugated estrogens 0.625/bazedoxifene 20 group, 46 (36%) in the conjugated estrogens 0.45/medroxyprogesterone acetate 1.5 group, and 36 (35%) in the placebo group). The most common criterion identified was absolute endometrial thickness > 4mm. [redacted] (b) (4)

The records were reviewed in a blinded manner for all subjects with potentially clinically important TVU findings. As outlined in the table below, 37 subjects had clinically important endometrial thickness > 8mm. Nine subjects had ovarian cysts > 20 mm, which were also reviewed as clinically important.

Table 24: Trial 31151A-304-WW: Subjects with Abnormal TVU Findings				
Test	**BZA 20 / CE0.45 N=361**	**BZA 20/ CE 0.625** (b) (4)	**CE0.45/ MPA 1.5 N=179**	**Placebo N=172**
	n (%)		**n (%)**	**n (%)**
Subjects with scans, N	**295**		**126**	**142**
Subjects with Potentially Clinically Important Findings				
Total with abnormalities	90 (30)	(b) (4)	46 (36)	36 (25)
Endometrial thickness, all	59 (20)		34 (27)	19 (13)
absolute value > 4mm	58 (20)		33 (26)	19 (13)
absolute value > 8mm	5 (2)		6 (5)	1 (1)
increase from baseline > 3mm	21 (7)		18 (14)	7 (5)
increase from baseline > 5mm	6 (2)		8 (6)	2 (1)
ovarian volume increase from baseline ≥ 2 cm^3	20 (8)		11 (11)	11 (9)
ovarian cysts visualized	27 (11)		15 (14)	8 (6)
Subjects with Clinically Important Findings				
Endometrial Thickness >8mm	6 (2)	(b) (4)	7 (4)	3 (2)
Ovarian Cyst >20mm	4 (1)		3 (2)	1 (1)
Source: CSR 73414 table 15.92				

Subjects who had TVU findings of endometrial thickness greater than 8 mm or a focal endometrial abnormality were to undergo hysteroscopy and hysteroscopic-directed endometrial biopsy rather than a routine endometrial biopsy. A total of 14 subjects had hysteroscopic-directed endometrial biopsies (3 in the conjugated estrogens 0.45/bazedoxifene 20, (b) (4) the conjugated estrogens 0.625/bazedoxifene 20 group, and 3 in the conjugated estrogens 0.45/ medroxyprogesterone acetate 1.5 group).

Summary: In the three studies evaluating endometrial safety of conjugated estrogens in combination with bazedoxifene, it is clear that bazedoxifene acts as an estrogen antagonist at the uterus and can provide endometrial protection in the presence of estrogen. However, based on the findings of all three studies, the dose of both the conjugated estrogen component and the bazedoxifene component are critical. I agree with Dr. Willett that the 24 month data must be considered for the chronic use indications proposed. Trial 3115A1-303 shows that 10 mg of bazedoxifene is insufficient to provide uterine protection when combined with both 0.625 mg and 0.45 mg conjugated estrogens. In both Trial 3115A1-303 and Trial 3115A1-3307, 20 mg of bazedoxifene appears to provide sufficient uterine protection in combination with both estrogen doses. (b) (4) . Based on the pharmacokinetic results of several trials, Formulation C, used in this trial, is estimated to provide 16 – 32% less bazedoxifene exposure than the product used in the other two studies. In the presence of a small decrease in bazedoxifene, the incidence of endometrial hyperplasia increased markedly. By 24 months, the incidence of endometrial hyperplasia was greater than (b) (4) when the goal is less than 1%.

Clinical pharmacology analyses indicate that bazedoxifene clearance is 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). These subjects would also be

expected to have higher endogenous estrogen levels. Dr. Fang Li of the pharmacometrics team conducted an analysis of endometrial hyperplasia cases based on body size. In trial 3115A1-303, 763 (35%) of enrolled subjects had a body mass index greater than 27. In subjects with endometrial hyperplasia, 64% had a body mass index greater than 27. This imbalance suggests that body size does play a role in development of endometrial hyperplasia. (b) (4)

I agree with Dr. Willett's and the Applicant's interpretation of the endometrial polyp findings, that conjugated estrogens 0.45/bazedoxifene 20 and conjugated estrogens 0.625/bazedoxifene 20 were associated with slightly higher incidence of endometrial polyps when compared to placebo. Labeling this finding may be beneficial to prescribers.

8.2 General Product Safety

The safety database for Duavee consists of the five phase 3 trials. On original NDA submission, different MedDRA versions were used for the different trials. The Applicant was asked to convert all trials to the same MedDRA version and resubmit the key individual trials and integrated safety summary tables. This review utilizes the data submitted November 29, 2012. The data presentation in this CDTL review differs from the style of data presentation in the primary clinical review. This reviewer combined the trials rather than discussing trials individually. A discussion of individual trial results and the primary clinical reviewer's findings will be included as appropriate. A total of 6041 postmenopausal women are included in the safety database including 1089 women treated with conjugated estrogens 0.45/bazedoxifene 20 and 1097 women treated with conjugated estrogens 0.625/bazedoxifene 20 treated for at least 6 months (Table 25). The number of subjects treated for at least a year was 987 in the conjugated estrogens 0.45/bazedoxifene 20 group and 1006 in the conjugated estrogens 0.625/bazedoxifene 20 group.

Table 25: Safety Database, Selected Dose Groups

	CE 0.45 / BZA 20	CE 0.625 / BZA 20	Placebo
N, treated	1585	1583	1241
N, treated for at least 6 months	1089	1097	
N treated for at least 1 year	987	1006	

Source: Table 1.3, SCS Supportive Tables

The primary Integrated Summary of Safety analyses includes Trials 3115A1-303, 3115A1-305, 3115A1-306, and 3115A1-3307. Trial 3115A1-304, is not included in the primary integrated summary of safety due to the lower bazedoxifene exposure that occurred with Formulation C in this trial. Notable findings from Trial 3115A1-304 and other studies are included in the discussion where appropriate. Table 26 displays the demographic data for subjects included in the safety analysis. The mean age of the population was 55 years with an age range of 40 – 75 years. The enrolled population was predominantly White with a mean body weight of 68 kg.

Table 26: Safety Database Demographics (Trials 303, 305, 306, 3307) , Selected Dose Groups			
	CE 0.45 / BZA 20	**CE 0.625 / BZA 20**	**Placebo**
N, treated	1224	1234	1069
Age, mean, years	55.33	55.05	55.26
Age, range, years	41 - 75	40 - 74	40 - 75
Age < 65 years	1189 (97)	1192 (97)	1023 (96)
Age ≥ 75 years	1 (0.1)	0	1 (0.1)
Race, Black, n (%)	102 (8)	104 (8)	109 (10)
Race, Other, n (%)	60 (5)	48 (4)	45 (4)
Race, White, n (%)	1062 (87)	1082 (88)	915 (86)
Weight, mean, kg	68.1	68.2	68.2
Weight, range, kg	40 - 106	38 - 108	39 - 105
Source: Table 1.10, SCS Supportive Tables			

Deaths: In the Duavee clinical program, 10 subjects died while participating in a Phase 3 clinical trial (see Table 109, page 171 of the Primary Clinical Review). Three deaths were accidental, one was attributed to cardiovascular disease, one was attributed to chronic obstructive pulmonary disease, two were attributed to underlying malignancy (acute myeloblastic leukemia and intracerebral hemorrhage secondary to metastatic lung cancer), and three listed unknown underlying cause. There is no concerning pattern noted.

Serious Adverse Events: Serious adverse events were reported by 42 (3%) subjects in the conjugated estrogens 0.45/bazedoxifene 20 group, 43 (4%) subjects in the conjugated estrogens 0.625/bazedoxifene 20 group, and 50 (5%) subjects in the placebo group (Table 27). The number of subjects reporting serious adverse events was small for each SOC, with the exception of Neoplasms (see Table below). Skin neoplasms (basal cell carcinoma of the skin, malignant melanoma and squamous cell carcinoma of the skin) was the most common preferred terms for each treatment group with other neoplasms occurring sporadically as single events.

As discussed in the primary clinical review, for Trial 3115A1-303, there is an apparent imbalance in the Cardiac SOC with more events in the 0.625 conjugated estrogen groups when compared to the other groups. However the number of events remains quite small, making interpretation difficult.

Table 27: Safety Database (Trials 303, 305, 306, 3307): Serious Adverse Events, Selected Dose Groups			
SOC, n (%)	**CE 0.45 / BZA 20**	**CE 0.625 / BZA 20**	**Placebo**
N, treated	1224	1234	1069
Any Serious Adverse Event	42 (3)	43 (4)	50 (5)
Blood and Lymphatic	2 (<1)	0	1 (<1)
Cardiac disorders	1 (<1)	4 (<1)	1 (<1)
Ear and Labyrinth	1 (<1)	2 (<1)	1 (<1)
Eye	1 (<1)	0	1 (<1)
Gastrointestinal	3 (<1)	4 (<1)	3 (<1)
General disorders	3 (<1)	4 (<1)	3 (<1)
Hepatobiliary Disorders	4 (<1)	1 (<1)	1 (<1)
Infections and Infestations	3 (<1)	6 (1)	7 (1)
Injury, Poisoning and Procedural	3 (<1)	6 (1)	4 (<1)
Investigations	0	1 (<1)	3 (<1)
Metabolism and Nutrition	1 (<1)	0	2 (<1)
Musculoskeletal	3 (<1)	4 (<1)	5 (<1)
Neoplasms	15 (1)	7 (1)	13 (1)
Nervous system	3 (<1)	3 (<1)	3 (<1)
Psychiatric	2 (<1)	1 (<1)	2 (<1)
Renal and Urinary	2 (<1)	1 (<1)	1 (<1)
Reproductive and Breast	1 (<1)	0	1 (<1)
Respiratory	2 (<1)	4 (<1)	3 (<1)
Skin and Subcutaneous	1 (<1)	0	0
Vascular	2 (<1)	2 (<1)	1 (<1)
Source: Table SCS Supportive Table using MedDRA 15.1, submitted 11/29 12			

Adverse Events Leading to Withdrawal: In the safety database, adverse events leading to withdrawal were reported by 8% of subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 8% of subjects in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and 10% of subjects in the placebo group (Table 28). Reporting rates were generally balanced among treatment groups. The most commonly involved SOCs were Vascular, Gastrointestinal, Disorders, and Nervous system disorders. The most common preferred terms were hot flush, headache, and nausea. Many of the Preferred Terms leading to withdrawal are associated with the efficacy parameters evaluated for Duavee, including hot flushes, endometrial hyperplasia, vaginal hemorrhage, and osteoporosis. In Trial 3115A1-303 Cardiac disorders exhibited some imbalances, with coronary artery disease reported in 5 subjects receiving 0.625 mg conjugated estrogens and not reported in any other treatment group. The reporting rate for the Cardiac SOC was balanced.

Table 28: Safety Database (Trials 303, 305, 306, 3307): Adverse Events Leading to Withdrawal, Selected Dose Groups			
SOC, n (%)	**CE 0.45 / BZA 20**	**CE 0.625 / BZA 20**	**Placebo**
N, treated	1224	1234	1069
Any Adverse Event	93 (8)	98 (8)	108 (10)
Blood and Lymphatic	0	0	1 (<1)
Cardiac disorders	4 (<1)	7 (1)	3 (<1)
Ear and Labyrinth	1 (<1)	3 (<1)	2 (<1)
Endocrine	0	1 (<1)	0
Eye	1 (<1)	2 (<1)	2 (<1)
Gastrointestinal	19 (2)	13 (1)	13 (1)
General disorders	10 (1)	15 (1)	11 (1)
Hepatobiliary Disorders	1 (<1)	0	1 (<1)
Immune system disorders	0	0	0
Infections and Infestations	4 (<1)	1 (<1)	0
Injury, Poisoning and Procedural	0	0	0
Investigations	9 (1)	11 (1)	5 (<1)
Metabolism and Nutrition	0	3 (<1)	0
Musculoskeletal	7 (1)	9 (1)	21 (2)
Neoplasms	6 (1)	3 (<1)	3 (<1)
Nervous system	9 (1)	17 (1)	15 (1)
Psychiatric	11 (1)	12 (1)	13 (1)
Renal and Urinary	0	2 (<1)	1 (<1)
Reproductive and Breast	12 (1)	9 (1)	13 (1)
Respiratory	1 (<1)	2 (<1)	3 (<1)
Skin and Subcutaneous	5 (<1)	5 (<1)	7 (1)
Vascular	14 (1)	13 (1)	22 (2)
Source: Table SCS Supportive Table using MedDRA 15.1, submitted 11/29 12			

Adverse Events: At least one adverse event was reported by 83% of subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 85% of subjects in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and 85% of subjects in the placebo group. Table 29 outlines the adverse events reported in the safety database by SOC. The most common SOCs for adverse events were Infections and Infestations, Musculoskeletal, and Gastrointestinal. As outlined in the primary clinical review pages 184 and 185, the most common preferred terms reported in Trials 3115A1-303 and 3115A1-3307 are headache, back pain, arthralgia, nasopharyngitis, pain in extremity, influenza, and myalgia. The adverse reactions table proposed by the Applicant appears appropriate and may be able to be shortened to only include reactions that are more common in the treatment group than the placebo group.

Table 29: Safety Database (Trials 303, 305, 306, 3307): Adverse Events, Selected Dose Groups			
SOC, PT >2%	**CE 0.45 / BZA 20**	**CE 0.625 / BZA 20**	**Placebo**
N, treated	1224	1234	1069
Any Adverse Event	1020 (83)	1049 (85)	907 (85)
Blood and Lymphatic	15 (1)	13 (1)	17 (2)
Cardiac disorders	36 (3)	28 (2)	30 (3)
Congenital and Genetic	1 (<1)	1 (<1)	1 (<1)
Ear and Labyrinth	58 (5)	58 (5)	49 (5)
Endocrine	15 (1)	9 (1)	9 (1)
Eye	49 (4)	53 (4)	55 (5)
Gastrointestinal	464 (38)	406 (33)	347 (32)
General disorders	205 (17)	222 (18)	202 (19)
Hepatobiliary Disorders	13 (1)	7 (1)	7 (1)
Immune system disorders	45 (4)	49 (4)	36 (3)
Infections and Infestations	555 (45)	539 (44)	493 (46)
Injury, Poisoning and Procedural	140 (11)	158 (13)	165 (15)
Investigations	171 (14)	163 (13)	159 (15)
Metabolism and Nutrition	70 (6)	66 (5)	69 (6)
Musculoskeletal	497 (41)	521 (42)	466 (44)
Neoplasms	41 (3)	29 (2)	34 (2)
Nervous system	373 (30)	371 (30)	366 (34)
Psychiatric	162 (13)	164 (13)	168 (16)
Renal and Urinary	57 (5)	69 (5)	59 (6)
Reproductive and Breast	200 (16)	210 (17)	179 (17)
Respiratory	235 (19)	212 (17)	160 (15)
Skin and Subcutaneous	183 (15)	181 (15)	138 (13)
Surgical and Medical procedures	2 (<1)	4 (<1)	5 (<1)
Vascular	105 (9)	95 (8)	110 (10)
Source: Table SCS Supportive Table using MedDRA 15.1, submitted 11/29 12			

Adverse Events of Special Interest:

Venous thromboembolism (VTE): Venous thromboembolism is a known adverse reaction for both estrogen and estrogen agonist/antagonists. In the Women's Health Initiative (WHI) estrogen alone substudy, the relative risk (95% CI) of deep venous thrombosis for conjugated estrogens was 1.47 (1.06, 2.06). For the estrogen plus progestin substudy, the relative risk was 1.95 (1.43, 2.67). In the bazedoxifene monotherapy trial 301, based on re-adjudicated data, the hazard ratio (95% CI) for venous thromboembolic events was 1.63 (0.68, 3.94) for bazedoxifene 20, 1.69 (0.7, 4.07) for bazedoxifene 40, and 1.14 (0.44, 2.96) for the active comparator, raloxifene. In the raloxifene osteoporosis treatment trial, the hazard ratio (95% CI) for venous thromboembolic events was 2.4 (1.2, 4.5).

In the Duavee clinical program, venous thromboembolic events from the five Phase 3 clinical studies were adjudicated by an independent Venous Thromboembolic Event Adjudication Committee which consisted of 3 consulting physicians with specialty in cardiology and internal medicine. There were seven reports of deep venous thrombosis among all treatment groups including 3 in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, none in the

conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and one in the placebo group. No events of retinal vein thrombosis, pulmonary embolism, or arterial thrombosis occurred.

When calculated in terms of women-years exposure, the VTE rate for the WHI estrogen only arm was 23 per 10,000 woman years compared to 15 per 10,000 woman years for placebo. For bazedoxifene monotherapy, based on study 3068A1-301, the VTE rate is 21-28 per 10,000 women-years for bazedoxifene 20mg and 14-17 per 10,000 women-years for placebo. Similar calculations were performed for the five trials in the Duavee clinical program where the VTE risk is calculated to be 0-3 per 10,000 women years for women receiving conjugated estrogen 0.45/bazedoxifene 20 or 0.625/bazedoxifene 20 and 6 per 10,000 women-years for placebo.

Coagulation studies and associated factors were evaluated closely, as discussed on page 178 of the primary clinical review. Consultation was also sought from the Division of Hematology Products for assistance in understanding if there is biologic plausibility for the findings based on interactions of these two agents on coagulation factors. There were no coagulation findings that could explain the findings seen in the clinical trial. One cannot conclude that the combination of conjugated estrogens and bazedoxifene are not associated with VTEs, therefore product labeling should include appropriate warnings and precautions.

Cerebrovascular events: In a trial of postmenopausal women with documented coronary artery disease, an increased risk of death due to stroke was observed during treatment with an estrogen agonist/antagonist. In the WHI estrogen-only substudy, an increased risk of stroke was observed. In the bazedoxifene monotherapy trial 301, based on re-adjudicated data, an increased risk of cerebrovascular events with bazedoxifene therapy was not observed.

In the Duavee clinical program, cerebrovascular events from the five Phase 3 clinical studies were adjudicated by an independent Cerebrovascular Event Adjudication Committee which consisted of 3 consulting physicians with specialty in neurology and neuroradiology and internal medicine. The incidence of adjudicated stroke was low, occurring in one subject in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, one subject in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and no subjects in the placebo group. Adjudicated transient ischemic events occurred in 2 subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group and no events in the conjugated estrogens 0.625mg/bazedoxifene 20 mg or placebo groups.

Cardiovascular events: In the WHI estrogen plus progestin substudy, there was an increased risk of coronary artery disease events compared to placebo. No overall difference was seen the in the WHI estrogen-only substudy. No overall difference in cardiovascular events was seen in the bazedoxifene monotherapy trial 301 upon readjudication.

In the Duavee clinical program, cardiovascular events from the five Phase 3 clinical studies were adjudicated by an independent Cardiovascular Event Adjudication Committee which consisted of 3 consulting physicians with specialty in cardiology and internal medicine. As outlined in the Table 30, coronary heart disease events were balanced across the treatment groups. Adjudicated coronary heart disease events were reported in 4 subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 4 subjects in the conjugated

estrogens 0.625mg/bazedoxifene 20 mg group, and 3 subjects in the placebo group. Adjudicated myocardial infarction was reported in 3 subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 1 subject in the conjugated estrogens 0.625mg/ bazedoxifene 20 mg group, and 2 subjects in the placebo group.. While there were sporadic imbalances in some cardiac preferred terms, when the safety database was evaluated, there was no concerning pattern or signal of increased cardiac risk.

Table 30: Safety Database (Trials 303, 304, 305, 306, 3307): Coronary Heart Disease and Angina Pectoris Adverse Events (Unadjudicated), Selected Dose Groups

	CE 0.45 / BZA 20	CE 0.625 / BZA 20	Placebo
N, treated	1585	1583	1241
Any CHD Event	4 (<1)	4 (<1)	5 (<1)
Arteriosclerosis coronary artery	0	0	1 (<1)
Coronary artery disease	3 (<1)	3 (<1)	0
Coronary artery insufficiency	0	0	1 (<1)
Myocardial infarction	2 (<1)	1 (<1)	2 (<1)
Silent myocardial infarction	1 (<1)	0	0
Sudden death	0	0	1 (<1)
Angina Pectoris	4 (<1)	3 (<1)	0
Source: Tables 2-29 and 2-33, Summary of Clinical Safety			

Reproductive disorders: Reproductive tissues including breast, uterus and ovaries are the main targets for estrogens and estrogen agonist/antagonists.

Breast: Mammography was performed in all five Phase 3 clinical trials at screening. Subjects with abnormal mammograms were not enrolled into the studies. On-treatment mammography was performed in at least a subset of subjects in the three trials with duration of one year or longer (3115A1-303, 3115A1-304, and 3115A1-3307). In these three trials, subjects with abnormal mammograms are enumerated in Table 31. The incidence of abnormal mammograms with the conjugated estrogens/bazedoxifene groups are similar to the active control groups – raloxifene: 5.3% at Month 12 and 3.4% at Month 24 in Trial 3115A1-303; bazedoxifene monotherapy: 0.8% in Trial 3115A1-304 and 7.8% in Trial 3115A1-3307; and conjugated estrogens 0.45/medroxyprogesterone: 1.5 1.4% in Trial 3115A1-304 and 12.9% in Trial 3115A1-3307. There is a marked difference between the results of these trials, most notably trials 3115A1-304 and 3115A1-3307, which used the same BI-RADS scoring to define abnormal. The reason for the differences between these two studies is not clear. Breast cancer was diagnosed in 6 subjects, 4 in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group and 2 in the placebo group.

Table 31: Safety Database (Trials 303, 304, 3307): Abnormal Mammogram, Cumulative Data up to Year 2, Selected Dose Groups						
	CE 0.45 / BZA 20		CE 0.625 / BZA 20		Placebo	
	N	n (%)	N	n (%)	N	n (%)
3115A1-303						
Month 12	330	12 (3.6)	305	12 (3.9)	307	13 (4.2)
Month 24	294	13 (4.4)	265	11 (4.2)	266	7 (2.6)
3115A1-304	305	2 (0.7)	300	3 (1.0)	149	4 (2.7)
3115A1-3307	370	37 (10.0)	412	24 (5.8)	398	21 (5.3)
Source: Tables 2-49 Summary of Clinical Safety						

Adverse events relating to the breast are outlined in the Table 32. Breast cyst is the most common adverse event related to breast mass reported.

Table 32: Safety Database (Trials 303, 304, 305, 306, 3307): Selected Breast Adverse Events (excluding breast cancer), Selected Dose Groups			
	CE 0.45 / BZA 20	CE 0.625 / BZA 20	Placebo
N, treated	1585	1583	1241
Any Breast Adverse Event	19 (1)	12 (1)	13 (1)
Breast neoplasm	5 (<1)	5 (<1)	3 (<1)
Breast cyst	7 (<1)	2 (<1)	4 (<1)
Breast dysplasia	1 (<1)	0	0
Breast fibrosis	0	1 (<1)	0
Breast hyperplasia	2 (<1)	0	1 (<1)
Breast mass	2 (<1)	3 (<1)	4 (<1)
Fibrocystic breast disease	2 (<1)	1 (<1)	1 (<1)
Source: Tables 2-29 and 2-33, Summary of Clinical Safety			

Ovaries and fallopian tubes: Adverse reactions relating to the ovaries and fallopian tubes were reported in 38 subjects (14 (1%) subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 12 (1%) subjects in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and 12 (1%) subjects in the placebo group. The most commonly reported event was ovarian cyst. Ovarian cancer was reported in 2 subjects, both in Trial 3115A1-303, one receiving conjugated estrogens 0.45mg/bazedoxifene 10 mg and one receiving conjugated estrogens 0.625mg/bazedoxifene 40 mg. One benign ovarian germ cell teratoma was reported in a placebo-treated subject in Trial3115A1-304.

Vaginal Bleeding: Vaginal bleeding and spotting are known adverse events with combination conjugated estrogen/medroxyprogesterone acetate products. Similarly, uterine protection using conjugated estrogen/estrogen agonist-antagonist products like bazedoxifene may provide incomplete protection from vaginal bleeding and spotting. Adverse reactions relating to vaginal bleeding were reported in 79 (5%) subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 72 (4%) subjects in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, 65 (5%) subjects in the placebo group, and 93 (23%) subjects in the conjugated estrogens 0.45/ medroxyprogesterone acetate 1.5 group. Further evaluation of subjects reporting adverse events of vaginal bleeding was not required. No subjects who reported vaginal bleeding required immediate medical attention.

Episodes of vaginal bleeding and in some trials the incidence of amenorrhea, were recorded daily by subjects enrolled in the clinical trials as a supportive efficacy parameter. In general, there were no differences in amenorrhea rates compared to placebo. In Trial3115A1-3307, the cumulative amenorrhea rates were higher for the conjugated estrogen/bazedoxifene treatment groups compared to the active control conjugated estrogens/medroxyprogesterone acetate (88% for the conjugated estrogens 0.45/bazedoxifene 20 group, 85% for the conjugated estrogen/bazedoxifene 0.625 group, 82% for the bazedoxifene only group, 54% for the conjugated estrogens 0.45/medroxyprogesterone acetate group and 84% for the placebo group).

Fracture: The trials conducted in the Duavee clinical program were not powered to assess fracture as a clinical efficacy endpoint. Fractures, reported as adverse events in the four main Phase 3 trials occurred in 22 (2%) subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 17 (1%) subjects in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and 18 (2%) subjects in the placebo group. The most common type of fractures are foot, rib, and wrist fractures. Foot fractures are generally not considered osteoporotic fragility fractures.

Lung cancer: A significant imbalance in lung cancers overall and lung adenocarcinomas was noted in the lasofoxifene clinical program. (b) (4) Estrogen receptor expression has been documented in normal lung and tumor tissue.

In the Duavee Phase 3 clinical trials, three subjects were reported to have lung cancers (one in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, one in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, one in the conjugated estrogens 0.625mg/bazedoxifene 100 mg group, and none in the placebo group. There is no evidence of lung cancer imbalances in the Duavee development program.

Ocular Adverse Events: Ocular events have been reported in the postmarketing period for bazedoxifene monotherapy which is marketed outside of the United States. In the five Duavee phase 3 clinical trials, SOC Eye Disorder events have been reported in 53 (3%) subjects in the conjugated estrogens 0.45mg/bazedoxifene 20 mg group, 53 (3%) subjects in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group, and 50 (4%) subjects in the placebo group. The most commonly reported preferred terms are dry eye, eye pain, and vision blurred.

Laboratory:
Laboratory Adverse Events: In the Duavee development program, three subjects reported laboratory adverse events where the laboratory value was also considered clinically important. One subject in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group developed

[6] Ali, G., Donati, V., Loggini, B., Servadio A, et al. Different estrogen receptor beta expression in distinct histiologic subtypes of lung adenocarcinoma (2008). Human Pathology, 39(10), 1465-73.

hypertriglyceridemia. One subject in the conjugated estrogens 0.625mg/bazedoxifene 20 mg group developed elevated liver enzymes. One subject in the placebo group developed elevated liver enzymes.

*Marked Laboratory Abnormalities***:** The Applicant utilized predetermined laboratory values to identify marked laboratory abnormalities of potential clinical importance. As outlined in the primary clinical review, pages 187-188, elevations in triglycerides and liver function test were evaluated closely and no imbalances were noted. Mean changes in laboratory values did not appear to be of clinical significance.

Summary: In this NDA, the safety database is adequate with over 1500 subjects per dose group receiving at least one dose, over 1000 patients per dose group receiving at least 6 months of therapy, and over 900 subjects per dose group receiving at least 1 year of therapy. The general safety profile of this estrogen plus estrogen agonist/antagonist product is consistent with other estrogen and estrogen agonist/antagonist products. The reasons for the very low rate of venous thrombotic events in all treatment groups including the placebo group are not clear and the data are difficult to interpret. Both conjugated estrogens and bazedoxifene are associated with increased rates of VTEs when prescribed as monotherapy. It is not known if these two agents interact in some way to produce an improved VTE signal.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this NDA.

10. Pediatrics

We are in agreement with the Applicant's request for a full waiver of the requirement to assess the safety and effectiveness of conjugated estrogens/bazedoxifene. The indications sought in this application include treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of moderate to severe vulvar and vaginal atrophy associated with menopause; and prevention of postmenopausal osteoporosis. None of these conditions occur in the pediatric population. The request was discussed and approved at the PeRC meeting April 3, 2013.

11. Other Relevant Regulatory Issues

Financial Disclosures: Financial Disclosure information has been reviewed by Dr. Whitaker, please see pages 25 -26 and Appendix 9.5 of the primary clinical review for complete details. Thirteen covered studies are included in the application and 215 investigators were identified. There were no employees of the Applicant included as investigators. One hundred and five investigators disclosed financial interests ranging from $26,000 to $626,000 mainly speakers bureau, honoraria, and consulting fees. Most investigators with financial interests enrolled

less (b) (4) of the trial population. I agree with Dr. Whitaker that the financial disclosure information should not affect the study results or approvability of the application.

Office of Scientific Investigations audits: The Office of Scientific Investigations conducted 9 site inspections including the bone density central read facility and Pfizer, Inc, where the endometrial biopsy samples were kept (Table 33). Most sites were classified No Action Indicated (NAI) or Voluntary Action Indication (VAI). Final determination of Dr. Christopher Hutchinson's site remains pending at this time.

Table 33: OSI Inspections and Final Classifications
Source: NDA 022247 Clinical Inspection Summary, page 5

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Edmund Baracat, M.D., Ph.D. 1017- Casa 6 -Paralso Sao Paulo, NA CEP04005-003	3115A1-303-US/EU/BR/ 447/ 889 (randomized)	6-17 May 2013	VAI
Sam StanleyMiller, M.D. 7711 Louis Pasteur Drive, Suite 300 San Antonio, TX 78229	3115A1-303-US/EU/BR/ 411/ 120	1–10 Apr 2013	VAI
John Christopher Gallagher, M.D. 601 North 30th Street, Suite 6712 Omaha, NE 68131	3115A1-303-US/EU/BR/ 375/ 73	11-15 Apr 2013	NAI
Christopher Hutchison, M.D. 4001 South 700 East, Suite 105 Salt Lake City, UT 84107	3115A1-305-US/ 538/ 26	10-29 Apr 2013	OAI. Pending final classification.
David Portman, M.D. 5965 East Broad Street, Suite 110 Columbus, OH 43213	3115A1-306-WW/ 649/ 21	11-15 Apr 2013	NAI
Phyllis Marx, M.D. 515 North State Street, Suite 2700 Chicago, IL 60654	3115A1-3307-WW/ 73/ 50	9-16 Apr 2013	NAI
David Portman, M.D. 99 North Brice Road, Suite 120 Columbus OH 43213	3115A1-3307-WW/ 37/ 25	3-11 Apr 2013	NAI
BMD Central Site, Helen Hayes Hospital 51 North, Route 9w West Haverstraw, NY 10993	3115A1-303-US/EU/BR and 3115A1-3307-WW	23 Apr-1 May 2013	NAI
Pfizer, Inc. 500 Arcola Road Collegeville, PA 19426-3982	3115A1-303-US/EU/BR and 3115A1-3307-WW	28 May-6 Jun 13	VAI

OSI has also been involved in preNDA discussions with the Applicant with regard to their processes used to ensure integrity and robustness of the clinical trial data. (b) (4)

In this NDA, the Applicant reports reviewing the source documentation at the South American sites that enrolled a large number of subjects for Trial 3115A1-303, site 447 enrolled 889 subjects and site 450 enrolled 307 subjects. The

Applicant reported that no additional serious adverse events or adverse events of special interest were identified. After audits of the South American sites, the Applicant initiated third party audits at 24 additional sites. Based on these findings, the Applicant requested a meeting to discuss missing source documentation, third party audits and content to include in the NDA submission. Agreements were reached regarding the information to be submitted, but no assurances were given regarding the approvability of the application.

Overall, complete or partial source documentation is missing for 286 (8%) subjects in Study 303, 5 (2%) subjects in Study 305, and 53 (8%) subjects in Study 306 and 8 (1%) subjects in Study 304. OSI is unable to verify results in subjects with missing source documentation and recommends consideration by the review team in that regard. The statistical team conducted sensitivity analyses removing subjects with missing source documentation for all key phase 3 clinical trials. Results are discussed throughout section 7 of this review where appropriate. OSI also recommended a sensitivity analysis excluding subjects from Dr. Hutchinson's site for Trial 3115A1-305. This analysis has been conducted and is discussed in section 7 of this review.

During an internal audit, critical GCP violations were found at Trial 3115A1-303 study site 326 (Dr. Joseph Sanfilippo, Pittsburgh Pennsylvania). This site enrolled 17 subjects (15 received study drug) into Trial 303. Based on the findings, the study site was terminated and notification was submitted to IND 62288 on March 29, 2004.

12. Labeling

Proprietary name: Duavee has been found acceptable. A final 90 day proprietary name review is pending at this time.

Carton and Container Labeling: Final agreement on carton and container labeling remains pending at the time of completion this review. Final comments to the Applicant for the carton and containers were conveyed on August 22, 2013. A response is pending.

(b) (4)

Patient labeling: Patient labeling is required for estrogen containing products and has been proposed by the Applicant.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:

I agree with the review team and recommend **Approval** for Duavee 0.45/20 (conjugated estrogens 0.45mg/bazedoxifene 20mg) for treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis.

I recommend a **Complete Response** for Duavee 0.625/20 (conjugated estrogens 0.625mg/bazedoxifene 20mg) for treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of moderate to severe vulvar and vaginal atrophy associated with menopause, and prevention of osteoporosis

.

Risk Benefit Assessment:

Duavee 0.45/20 (conjugated estrogens 0.45/bazedoxifene 20): After excluding subjects with missing source documentation and subjects for whom data cannot be relied upon, I agree with the review team that Duavee 0.45/20 is efficacious in reducing the incidence and severity of moderate and severe hot flushes associated with menopause and for prevention of postmenopausal osteoporosis. The placebo-subtracted treatment difference in the mean number of daily hot flushes is -2.9 at Week 4 and -2.8 at Week 12. For average severity score, the placebo-subtracted treatment difference is -0.45 at Week 4 and -0.65 at Week 12. The placebo-subtracted mean change in lumbar spine bone mineral density at Month 24 is 3.1% for women greater than 5 years post menopause and 3.6% in women less than 5 years post menopause. The mean change at the total hip at Month 24 is 1.7% for women greater than 5 years post menopause and 2.0% in women less than 5 years post menopause.

Endometrial safety has been adequately demonstrated for the Duavee 0.45/20 dose. Based on the general safety profile of the product, Duavee 0.45/20 is well tolerated. The safety profile is similar to that of estrogens and estrogen agonist/antagonists. No new safety signals were revealed in the clinical program.

I agree with the review team that Duavee 0.45/20 for treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis are recommended for Approval.

Duavee 0.625/20 (conjugated estrogens 0.625/bazedoxifene 20): (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

I agree with the review team that Duavee 0.625/20 for treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of moderate to severe vulvar and vaginal atrophy associated with menopause, and prevention of postmenopausal osteoporosis is recommended for a Complete Response (b) (4)

Recommendation for Postmarketing Risk Evaluation and Management Strategies:

Postmarketing Risk Evaluation and Management Strategies are not necessary for the approval of this combination product.

Recommendation for other Postmarketing Requirements and Commitments:

There are no Postmarketing Requirements or Commitments recommended for this combination product.

Recommended Comments to Applicant:
Clinical/Statistical
Deficiencies:

(b) (4)

Information needed to address the deficiencies:

(b) (4)

(b) (4)

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

/s/

THERESA E KEHOE
08/28/2013

HYLTON V JOFFE
08/28/2013
Please see Division Director memorandum