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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number: 022247 / N000

Drug Name: Conjugated estrogens /bazedoxifene tablet

Indication(s): Treatment of moderate to severe vulvar and vaginal atrophy (VVA) associated with the menopause

Applicant: Wyeth Pharmaceuticals Inc.

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Keywords: NDA review, clinical studies, ANCOVA, Cochran-Mantel-Haenszel

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/s/

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06/05/2013

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U.S. Department of Health and Human Services
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Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/eCTD Sequence #: 22247 / 0000

Drug Name: conjugated estrogens / bazedoxifene

Indication(s): Prevention of postmenopausal osteoporosis

Applicant: Wyeth Pharmaceuticals, Inc. (A wholly owned subsidiary of Pfizer Inc.)

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Key Words: Clinical studies, NDA review, Multinational Study

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1. EXECUTIVE SUMMARY

The two submitted studies provide supportive evidence demonstrating the efficacy of two dosages of bazedoxifene/conjugated estrogens (BZA/CE) for the prevention of osteoporosis in postmenopausal women based on the improvement in lumbar spine bone mineral density (primary endpoint) and total hip bone mineral density (important secondary endpoint). Overall, there was an increase in the bone mineral density (BMD) of the lumbar spine and total hip with BZA/CE use compared to placebo.

The evidence is based on the results of comparisons between BZA/CE and placebo with respect to percent change from baseline after treatment in: 1) lumbar spine BMD and 2) total hip BMD from two multinational, randomized, multicenter, double-blind, parallel-group, placebo- and active-controlled studies. The focus is on women who were no more than 5 years postmenopausal.

For the primary endpoint, compared to placebo, both BZA/CE dosages increased the mean percent change from baseline in lumbar spine BMD by (b) (4) for BZA 20 mg/CE 0.625 mg and by 3.6% for BZA 20 mg/CE 0.45 mg in one study after 2 years of treatment and by (b) (4) for BZA 20 mg/CE 0.625 mg and by 1.5% for BZA 20 mg/CE 0.45 mg in the second study after 1 year of treatment.

For the important secondary endpoint, compared to placebo, both BZA/CE dosages increased the mean percent change from baseline in total hip BMD by (b) (4) for BZA 20 mg/CE 0.625 mg and by 1.9% for BZA 20 mg/CE 0.45 mg in one study after 2 years of treatment and by (b) (4) for BZA 20 mg/CE 0.625 mg and by 1.2% for BZA 20 mg/CE 0.45 mg in the second study after 1 year of treatment.

2. INTRODUCTION

2.1 Overview

This is a submission of two multinational, randomized, multicenter, double-blind, parallel-group, placebo- and active-controlled studies evaluating the efficacy and safety of various dosages of bazedoxifene/conjugated estrogens (BZA/CE) on the incidence of endometrial hyperplasia (safety), prevention of postmenopausal osteoporosis, treatment of vasomotor symptoms, and treatment of vulvar-vaginal atrophy in postmenopausal women. Table 2.1 presents a brief summary of these two studies. The studies were designed as large studies with various substudies for the different indications. This review will only focus on the prevention of postmenopausal osteoporosis indication.

Table 2.1
Brief Summary of Clinical Studies for BZA/CE

Study Number (Country) Dates of Study Conduct	Subject Population	Treatment ³	ITT ^{1,2} Population	Design ³
3115A1-303 (Belgium, Brazil, Finland, Italy, Netherlands, Norway, Poland, Spain, United States) April 2002 to January 2006	Healthy, postmenopausal women with uterus	BZA 10 mg/CE 0.45 mg BZA 20 mg/CE 0.45 mg BZA 40 mg/CE 0.45 mg (b) (4) Raloxifene 60 mg Placebo Total	290 293 284 (b) (4) 295 292 2315	DB, R, PC, PG, MC, MN, 2-year
3115A1-3307 (Argentina, Australia, Chile, Colombia, Denmark, Finland, Hungary, Mexico, New Zealand, Norway, Poland, United States) January 2009 to February 2011	Healthy, postmenopausal women with uterus	BZA 20 mg/CE 0.45 mg (b) (4) MPA 1.5 mg/CE 0.45 mg BZA 20 mg Placebo Total	135 (b) (4) 70 73 158 590	DB, R, PC, PG, MC, MN, 1-year

Source: Statistical Reviewer's listing.

¹ ITT = Intent to Treat, received investigational product

² The number of subjects for each study refer only to those who were part of the osteoporosis prevention substudy.

³ BZA = Bazedoxifene, CE = Conjugated Estrogens, MPA = Medroxy Progesterone, DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter, MN = Multinational

The proposed indication is:

BZA/CE is indicated for prevention of postmenopausal osteoporosis in women with a uterus.

BZA/CE is a combination selective estrogen receptor modulator and conjugated estrogen product and according to the Applicant:

Conjugated estrogens (Premarin) successfully treat symptoms of the menopause and prevent postmenopausal osteoporosis. Unopposed estrogens, however, stimulates the endometrium and may lead to endometrial hyperplasia. Combining progestin with estrogen reduces stimulation of the endometrium. Clinical evidence suggests that combining bazedoxifene, a selective estrogen receptor modulator (SERM), with estrogen may reduce the stimulation of the endometrium. Bazedoxifene shows tissue-specific agonist/antagonist activity. Clinical evidence has suggested that regimens combining bazedoxifene with CE are effective in relieving vasomotor symptoms and favorably altering biochemical indices of bone metabolism while also providing favorable metabolic, uterine bleeding, and adverse event profiles. In this study, raloxifene serves as a reference to provide data on non-hyperplastic endometrial changes associated with its use.¹ Additionally, as raloxifene is indicated for the prevention of postmenopausal osteoporosis, it provides a reference for bone mineral density changes (*source: page 8 of the Statistical Analysis Plan for Study 303*).

For the prevention of postmenopausal osteoporosis indication, these two studies (3115A1-303 and 3115A1-3307) were designed to compare the effects of BZA/CE versus placebo on lumbar spine bone mineral density (BMD) and total hip BMD after one or two years of treatment. This review will focus on the results for the to-be-marketed doses of BZA 20 mg/CE 0.625 mg and BZA 20 mg/CE 0.45.

2.2 Data Sources

The study report and additional information for these studies were submitted electronically. The submitted SAS data sets for each study were complete and well documented. These items are located in the CDER Electronic Document Room as described below:

- The complete study reports are located at <\\Cdsub1\evsprod\NDA022247\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\osteoporosis\5351-stud-rep-contr\study-3115a1-303> and <\\Cdsub1\evsprod\NDA022247\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\osteoporosis\5351-stud-rep-contr\study-3115a1-3307> under submission date 9-26-2012 (eCTD Sequence Number 0000).
- Raw and derived data sets used for analysis and the data set define files and programs are located at <\\Cdsub1\evsprod\NDA022247\0000\m5\datasets\study-3115a1-303> and <\\Cdsub1\evsprod\NDA022247\0000\m5\datasets\study-3115a1-3307> under submission date 9-26-2012 (eCTD Sequence Number 0000).
- Additional information used in this review is located at <\\Cdsub1\evsprod\NDA022247> under submissions dated 12-5-2012, 2-7-2013, 2-19-2013, 3-1-2013, 4-3-2013, 4-9-2013, 5-9-2013, and 5-15-2013 (eCTD Sequence Numbers 0010, 0017, 0018, 0020, 0025, 0022, 0034, and 0036, respectively).

3. STATISTICAL EVALUATION

This section describes the study design, data and analysis quality, evaluation of efficacy, and study results.

3.1 Data and Analysis Quality

The submitted datasets were well documented and easily accessible. The derived efficacy datasets used for the primary efficacy analysis can be created from the raw datasets. This review reproduced the primary efficacy results as presented in each study report from the derived efficacy datasets based on an ANCOVA model with treatment and region as factors and baseline BMD and years since menopause as covariates with study sites grouped into US and non-US regions (see sections 3.2.2 and 3.2.4). The final statistical analysis plan was submitted prior to unblinding and there were no changes to the pre-specified primary and secondary analyses as presented in the protocol.

There was one statistical analysis issue identified in this submission for the prevention of postmenopausal osteoporosis indication. During the pre-NDA process for this application, the Division learned of multiple

problems with the availability/existence of source documents. The CDER Office of Scientific Investigations communicated with the Applicant to ascertain what documents were missing and the extent of missing documents. This issue affected study 3115A1-303 but not study 3115A1-3307.

The Division sent an information request to the Applicant on 12-12-2012 to:

- Provide a listing (including subject identification) and description of which source documents are missing for all subjects with missing source documents.
- Provide safety and efficacy analyses excluding all subjects with missing source documentation.

The Applicant responded to these requests on 2-19-2013 (eCTD sequence number 0018). The Division sent another information request to the Applicant on 2-21-2013 to:

- Submit for each study a SAS dataset with the subject identification numbers for those subjects with completely or partially missing source document information.

The Applicant responded to this request on 3-1-2013 (eCTD sequence number 0020). Based on this information, I performed a sensitivity analysis of the efficacy data for lumbar spine BMD and total hip BMD that excluded those subjects with missing source documents. There were few subjects with missing source documents (range from 3% to 7%, see section 3.2.5). The impact of missing source documents did not appreciably affect the results of the lumbar spine BMD and total hip BMD analyses in study 3115A1-303 because the results of the analyses that included and excluded those subjects with missing source documents were similar (see section 3.2.6).

Otherwise, the Applicant adhered to statistical methods for the primary and important secondary endpoints as specified in the protocol and Statistical Analysis Plan.

3.2 Evaluation of Efficacy

The Applicant has submitted two clinical studies (3115A1-303 and 3115A1-3307) designed to demonstrate the efficacy and safety of bazedoxifene/conjugated estrogens (BZA/CE) compared to placebo for the prevention of osteoporosis in postmenopausal women. The review of both studies will focus on the primary BMD endpoint at the lumbar spine and important secondary BMD endpoint at the total hip.

The design, endpoints, and statistical methodologies of each study are presented first (sections 3.2.1 through 3.2.4) and followed by the results of each study (sections 3.2.5 through 3.2.8).

3.2.1 Study 3115A1-303: Study Design and Endpoints

The primary study objective was to evaluate the effects of six dosages of bazedoxifene/conjugated estrogens (BZA/CE) on the incidence of endometrial hyperplasia in postmenopausal women at year 1. The secondary objective was to evaluate the efficacy of various dosages of BZA/CE combinations in preventing postmenopausal osteoporosis at year 2, and to evaluate the effects of BZA/CE combinations on vaginal atrophy, uterine bleeding, and vasomotor symptoms in postmenopausal women.

This was a 24-month, 8-arm, outpatient, multicenter, multinational, double-blind, randomized, placebo- and raloxifene-controlled phase 3 study to assess the safety and efficacy of six dosages of BZA/CE in postmenopausal women. The efficacy of BZA/CE for osteoporosis prevention was assessed in two substudies: the Osteoporosis Prevention I Substudy (women >5 years postmenopausal); and the Osteoporosis Prevention II and Metabolic Substudy (women ≥ 1 year and ≤ 5 years postmenopausal). These studies are referred to as substudy I and substudy II for the remainder of this review.

Subjects were healthy women, 40 to 75 years of age, who were clinically diagnosed as postmenopausal with a body mass index of no more than 32.2 kg/m². All subjects had to have an intact uterus and acceptable endometrial biopsy results at screening. Women in substudy I had to be more than 5 years postmenopausal, have a bone mineral density (BMD) T-score at the lumbar spine or total hip between -1 and -2.5 (inclusive), and have at least 1 additional risk factor for osteoporosis; those in substudy II had to be at least 1 year and no more than 5 years postmenopausal, and have at least 1 additional risk factor for osteoporosis.

Randomization was balanced by site with treatment randomized using permuted blocks of 8, with 1 block for each treatment group. Subjects were equally randomized to one of the following eight treatment groups:

BZA 10 mg/CE 0.625 mg	BZA 10 mg/CE 0.45 mg	Raloxifene 60 mg
BZA 20 mg/CE 0.625 mg	BZA 20 mg/CE 0.45 mg	Placebo
BZA 40 mg/CE 0.625 mg	BZA 40 mg/CE 0.45 mg	

All test products were provided as matching over-encapsulated tablets. Each subject took one capsule orally, once daily, for two years. Subjects were to maintain consistent intake of dietary and supplemental calcium and vitamin D throughout the study.

The overall study primary endpoint was the incidence of endometrial hyperplasia at year 1 and was the basis for the overall sample size. The main primary efficacy endpoint for the two substudies was the mean percent change from baseline at year 2 in lumbar spine BMD and the important secondary efficacy endpoint is the mean change from baseline at year 2 in total hip BMD. The sample sizes for the BMD endpoints were adequate for the hypotheses of interest (see section 3.2.2). Analyses were done separately for each substudy. The analysis for substudy II (women ≥ 1 year and ≤ 5 years postmenopausal) was considered of primary interest.

BMD measurements of the lumbar spine and hip (total hip, femoral neck, trochanter and intertrochanteric area) were measured by dual-energy x-ray absorptiometry (DXA), at least twice during screening, once during month 6, twice during month 12, once during month 18 and twice during month 24 or early withdrawal occurring more than 13 weeks after previous BMD measurement. All DXA scans were evaluated centrally.

Vertebrae L2 to L4 were measured unless one of them was abnormal, in which case L1 was measured. The two prestudy scans of the lumbar spine must have differed by less than 5%; otherwise a third scan was acquired. The findings of the three scans were compared, and the two scans closest to the mean of the three, and within 5% of each other, were reported as the baseline value. The two prestudy scans of the total hip must have differed by less than 7.5%; otherwise a third scan was acquired. The findings of the three scans were compared, and the two scans closest to the mean of the three, and within 7.5% of each other, were reported as the baseline value.

Similarly, the month 24 value was computed as the mean of the two measurements taken if two measurements were taken. If more than 2 measurements were reported, then the two measurements closest to the mean of all the measurements were used to compute the on-therapy value. If only one measurement was taken at baseline or month 24, then that single value was used for analysis.

3.2.2 Study 3115A1-303: Statistical Methodologies

The primary analysis population was the modified-intent-to-treat (MITT) population, defined as all randomized subjects who took at least one dose of test article and had a baseline and at least one on-therapy BMD value for the area of interest (lumbar spine or total hip). Efficacy analysis was done separately for each substudy.

Analysis of Lumbar Spine

The primary efficacy endpoint, the percent change from baseline in lumbar spine BMD at month 24, was analyzed using last-observation-carried forward (LOCF) on the MITT population and an analysis of covariance (ANCOVA) model including treatment and region as factors and baseline BMD and years since menopause as covariates with study sites grouped into US and non-US regions. The ANCOVA model had the following form:

$$\text{Percent change from baseline} = \text{treatment} + \text{region} + \text{baseline BMD value} + \text{years since menopause}$$

The LOCF method used each subject's last on-therapy BMD evaluation was used to compute the percent change from baseline at month 24 as follows:

$$\text{Percent change from baseline} = 100\% * (\text{BMD month 24}_{\text{LOCF}} - \text{BMD baseline}) / \text{BMD baseline}$$

Analysis of Total Hip

The percent change from baseline at month 24 for total hip BMD was analyzed using the same ANCOVA model as that for lumbar spine BMD using the MITT population with LOCF.

Interim Analysis

An interim analysis was done when subjects completed or withdrew before the first year of study. The purpose of the analysis was for planning which dose or doses to use for a subsequent trial, not for early stopping of this study and declaring success. Due to the planned interim analysis at year 1, the significance level for the interim analysis of BMD at year 1 was 0.005, and the significance level for the final analysis at year 2 was 0.048 (2-sided) (O'Brien-Fleming, 1979). Interim analysis was done for BMD at the spine and total hip at months 6 and 12 for the MITT population using ANCOVA on the percent change from baseline with and without LOCF.

Testing Procedure

The final analysis was done in a stepwise manner to control the overall type I error rate. The hyperplasia rate was tested at a 0.05 significance level (see Appendix for details of this testing procedure). If the hyperplasia rate met the acceptability criteria, then BMD endpoints were compared at the two-sided 0.048 level significance level. Finally, if the BMD endpoints were statistically significant, then the daily mean number and severity of hot flushes were compared at the 0.05 significance level.

No interim analysis adjustment for hyperplasia and vasomotor symptoms was necessary since the initial analysis at year 1 was the primary analysis of interest. All pairwise comparisons were done using the two-sided t-test (based on adjusted means and pooled error term obtained from the ANCOVA) at the 0.048 significance level.

For the primary analysis of lumbar spine at month 24, pairwise comparisons between active treatment group and placebo, based on the ANCOVA model, were done in a sequential manner to address the multiplicity issue when testing six different treatment groups. The regimens with the CE 0.625 mg dose were tested first at the 0.048 level and proceeded as shown below.

BZA 10 mg/CE 0.625 mg (Regimen 1)
↓
BZA 20 mg/CE 0.625 mg (Regimen 2)
↓
BZA 40 mg/CE 0.625 mg (Regimen 3)

If Regimen 1 was found to be significantly different from placebo, then Regimen 2 was compared to placebo. If Regimen 2 was significantly different from placebo, then Regimen 3 was compared to placebo.

If a significant difference was found between the BZA 10 mg/CE 0.625 mg group and placebo, then comparisons to placebo for combinations that include the 0.45 mg dose of CE were similarly tested in a sequential manner as shown below.

BZA 10 mg/CE 0.45 mg (Regimen 4)
↓
BZA 20 mg/CE 0.45 mg (Regimen 5)
↓
BZA 40 mg/CE 0.45 mg (Regimen 6)

This procedure was first applied to substudy I. If a significant difference between BZA 10 mg/CE 0.625 mg and placebo was found, then the same sequential process was followed for testing in substudy II.

Sample Size

Overall, approximately 3000 subjects at about 94 sites (8 treatment groups of 375 subjects) were enrolled to complete about 2400 subjects (8 treatment groups of 300 subjects) at 1 year and about 1920 subjects (8 treatment groups of 240) at 2 years. The main study included two substudies, as described below. Sites were selected to conduct one study group.

- Main Study: Approximately 29 sites each enrolled about 32 subjects (928 total subjects or 8 treatment groups of 116 subjects).
- Substudy I: Approximately 40 sites each enrolled about 32 subjects (1280 total subjects or 8 treatment groups of 160 subjects).

- Substudy II: Approximately 25 sites each enrolled about 32 subjects (800 total subjects or 8 treatment groups of 100 subjects).

The overall study sample size was based on the incidence rate of endometrial hyperplasia at 24 months and resulted in a sample size of 375 per group to assure 300 evaluable subjects per group.

For substudy II, sample size was based on the mean percent change from baseline in lumbar spine BMD at 24 months, assuming a standard deviation of 3.5%, 90% power, difference between groups of 2.0%, and significance level of 0.048 (adjusted significance level due to interim analysis). This resulted in 67 subjects per group. In addition, it was expected that the difference between groups may be smaller for total hip, so 100 per group were enrolled in order to provide adequate power for total hip. This provided about 90 per group for inclusion in the ITT analysis.

In substudy I, the difference between groups in lumbar spine BMD was expected to be at least 2%, however, the difference in total hip BMD could be as low as 1.5%. Therefore, sample size was based on the mean percent change from baseline in total hip BMD at 24 months, assuming a standard deviation of 3.5%, 90% power, difference between groups of 1.5%, and significance level of 0.048. This resulted in 117 subjects per group. But enrolling 160 per group provided at least 90% power for both lumbar spine and total hip BMD endpoints.

3.2.3 Study 3115A1-3307: Study Design and Endpoints

The co-primary study objectives were 1) to evaluate the safety of two dosages of bazedoxifene/conjugated estrogens (BZA/CE) on the incidence of endometrial hyperplasia in postmenopausal women at year 1 and 2) to evaluate the efficacy of BZA/CE combinations in preventing osteoporosis at year 1.

This was a 12-month, 5-arm, outpatient, multicenter, multinational, double-blind, randomized, placebo- and active-controlled phase 3 study to assess the safety and efficacy of two dosages of BZA/CE in postmenopausal women. This main study included a breast density substudy, an osteoporosis substudy, and a sleep substudy. The efficacy of BZA/CE for osteoporosis prevention was assessed in the osteoporosis substudy.

Subjects were healthy women, 40 to 65 years of age, who were clinically diagnosed as postmenopausal with a body mass index of no more than 34.0 kg/m². All subjects had to have an intact uterus and acceptable endometrial biopsy results at screening. Women in the osteoporosis substudy had to be no more than 5 years postmenopausal and had two evaluable BMD scans of the lumbar spine and total hip that differed by less than 5% and 7.5%, respectively.

All subjects participated in the main study and were randomized and stratified by whether they were in the osteoporosis substudy or not. Eligible subjects could also participate in the sleep and breast density substudies. Randomization was stratified by whether or not a subject participated in the osteoporosis substudy and balanced by study site. In both the main and osteoporosis substudy, subjects were randomized to one of the following five treatment groups in a 2:2:1:1:2 ratio, respectively:

- BZA 20 mg/CE 0.625 mg
- BZA 20 mg/CE 0.45 mg
- BZA 20 mg
- Medroxy progesterone (MPA) 1.5 mg/CE 0.45 mg
- Placebo

All test products were provided as matching over-encapsulated tablets. Each subject took one capsule orally, once daily, for one year. Subjects were to maintain consistent intake of dietary and supplemental calcium and vitamin D throughout the study.

The overall study primary endpoint was the incidence of endometrial hyperplasia at year 1 and was the basis for the overall sample size. The main primary efficacy endpoint for the osteoporosis substudy was the mean percent

change from baseline at year 1 in lumbar spine BMD and the important secondary efficacy endpoint is the mean change from baseline at year 1 in total hip BMD.

BMD measurements of the lumbar spine and hip (total hip, femoral neck, trochanter and intertrochanteric area) were measured by dual-energy x-ray absorptiometry (DXA), at least twice during screening, once during month 6, and twice during month 12 or early withdrawal occurring more than 26 weeks after previous BMD measurement. All DXA scans were evaluated centrally.

Vertebrae L2 to L4 were measured unless one of them was abnormal, in which case L1 was measured. The two prestudy scans of the lumbar spine must have differed by less than 5%; otherwise a third scan was acquired. The findings of the three scans were compared, and the two scans closest to the mean of the three, and within 5% of each other, were reported as the baseline value. The two prestudy scans of the total hip must have differed by less than 7.5%; otherwise a third scan was acquired. The findings of the three scans were compared, and the two scans closest to the mean of the three, and within 7.5% of each other, were reported as the baseline value.

Similarly, the month 12 value was computed as the mean of the two measurements taken if two measurements were taken. If more than 2 measurements were reported, then the two measurements closest to the mean of all the measurements were used to compute the on-therapy value. If only one measurement was taken at baseline or month 12, then that single value was used for analysis.

3.2.4 Study 3115A1-3307: Statistical Methodologies

The primary analysis population was the modified-intent-to-treat (MITT) population, defined as all randomized subjects who took at least one dose of test article and had a baseline and at least one on-therapy BMD value for the area of interest (spine or hip).

Analyses of Lumbar Spine and Total Hip

The primary efficacy endpoint, the percent change from baseline in lumbar spine BMD at month 12, and the important secondary efficacy endpoint, the percent change from baseline for total hip BMD at month 12, were analyzed with the same ANCOVA model as previously described (see section 3.3.2).

Testing Procedure

The two primary endpoints, the incidence rate of endometrial hyperplasia and the percent change in lumbar spine BMD at year 1, were analyzed at different times. Because subjects in the osteoporosis substudy were completing the study in advance of the subjects not in that substudy, the final BMD data, the key efficacy endpoint for this substudy were available earlier. Therefore, the final BMD analyses were performed when the final data for the osteoporosis substudy became available. When the main study was completed, all other endpoints, including the other primary endpoint, endometrial hyperplasia, were evaluated.

Comparisons between the BZA/CE groups and the placebo group were of primary interest. In addition, the BZA 20 mg group and MPA/CE group were compared to placebo. All pairwise comparisons were done using the two-sided t-test (based on adjusted means and pooled error term obtained from the ANCOVA) at the 0.05 significance level.

For the primary analysis of lumbar spine at month 12, pairwise comparisons between the BZA/CE groups and placebo were done in a sequential manner to address the multiplicity issue when testing two different treatment groups. The BZA 20 mg/CE 0.625 mg treatment group was first compared to placebo. If the BZA/CE 0.625 mg group is found to be significantly better than placebo at the 0.05 level, then BZA 20 mg/CE 0.45 mg was compared to placebo as shown below.

BZA 20 mg/CE 0.625 mg
↓
BZA 20 mg/CE 0.45 mg

Sample Size

Approximately 1720 subjects (3 treatment groups of 430 subjects and 2 treatment groups of 215 subjects) were enrolled in the main study to complete about 1200 subjects (3 treatment groups of 300 subjects and 2 treatment groups of 150 subjects). Overall, approximately 150 sites each enrolled about an average of 12 subjects. Of these 1720 subjects in the main study, approximately 600 subjects participated in the osteoporosis substudy (3 treatment groups of 150 subjects and 2 treatment groups of 75 subjects) to complete about 512 subjects (3 treatment groups of 128 subjects and 2 treatment groups of 64 subjects).

The overall study sample size was based on the incidence rate of endometrial hyperplasia at 12 months and resulted in a sample size of 430 subjects per group for three treatments to assure 300 evaluable subjects per group and 215 subjects per group for two treatments to assure 150 evaluable subjects per group.

For the osteoporosis substudy, sample size was based on the mean percent change from baseline in lumbar spine BMD at 12 months, assuming a standard deviation of 3.5%, 90% power, difference between groups of 2.5%, and significance level of 0.05. This resulted in 42 subjects per group. In addition, it was expected that for total hip, the difference between groups was 1.5% with a standard deviation of 3.0%. Assuming 90% power, this resulted in 84 subjects per group. Based on these two calculations, a total of 150 subjects in the placebo and each of the BZA/CE groups and 75 subjects in the BZA and MPA/CE groups, respectively, were enrolled. It was assumed that if 85% of these subjects had at least one post-baseline BMD assessment for analysis, then each comparison of treatment to placebo would have at least 90% power.

3.2.5 Study 3115A1-303 Subject Disposition and Baseline Characteristics

For study 3115A1-303, overall, a total of 3544 subjects were randomly assigned to eight treatment groups with 1454 subjects included in substudy I [822 from Brazil (1 site) and 632 from USA (37 sites)] and 861 subjects included in substudy II [303 from Brazil (1 site), 34 from EU (4 sites) and 524 from USA (28 sites)].

Overall, 3397 subjects took at least 1 dose of test article with 1454 dosed subjects included in substudy I and 861 dosed subjects included in substudy II. Tables 3.1 and 3.2 present the number of randomized subjects and their disposition for each substudy for the four treatment groups of interest.

In substudy I, a total of 727 subjects were randomized to and took study product for the four groups of interest; (b) (4) 182 to the BZA 20 mg/ CE 0.45 mg group, 188 to the Raloxifene group, and 184 to the placebo group. For the primary efficacy endpoint, 642 of the 727 randomized subjects were included in the MITT analysis. For a sensitivity analysis of the primary efficacy endpoint, 28 subjects in the MITT population (which is 3% to 5% of the subjects across the four treatment groups) had missing source documentation and were excluded. The Clinical Reviewer concurred with this decision. The study results were not affected by the removal of these 28 subjects because analyses including all subjects gave similar results.

Discontinuation rates ranged from 25.4% to 28.2% in all the active treatment groups and the rate was 34.8% in the placebo group. The primary reasons for study discontinuation were adverse event (10.6% to 13.7% for active treatment and 15.2% for placebo), withdrawal of consent (6.4% to 10.1% for active treatment and 10.3% for placebo), and other (3.7% to 4.6% for active treatment and 4.3% for placebo).

Table 3.1
Study 3115A1-303: Randomization and Disposition of Substudy I Subjects

	BZA 20 mg/ CE 0.625 mg	BZA 20 mg/ CE 0.45 mg	Raloxifene 60 mg	Placebo
Number Randomized and Took Study Product (ITT)	(b) (4)	182	188	184
Completed n (%)*		131 (72.0)	135 (71.8)	120 (65.2)
Discontinued n (%)*		51 (28.0)	53 (28.2)	64 (34.8)
Number in MITT Population, Lumbar Spine BMD		160 (87.9)	164 (87.2)	159 (86.4)
Number Without Missing Source Documentation (MITT)		155 (85.2)	157 (83.5)	151 (82.1)
Primary Reason for Discontinuation n (%)*:				
Adverse Event		25 (13.7)	20 (10.6)	28 (15.2)
Death		0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-up		4 (2.2)	4 (2.1)	3 (1.6)
Other		7 (3.8)	7 (3.7)	8 (4.3)
Protocol Deviation		0 (0.0)	1 (0.5)	5 (2.7)
Subject Withdrew Consent		15 (8.2)	19 (10.1)	19 (10.3)
Lack of efficacy		0 (0.0)	2 (0.0)	1 (0.5)

Source: Table 8-2, page 77, Study 3315A1-303 report and Statistical Reviewer's listing based on SAS datasets DS and SCE1-DS.

* With respect to number of randomized subjects who took study product.

All groups in substudy I were similar in baseline and demographic characteristics based on the ITT population. The majority of subjects were Caucasian (>71%) and had a mean age of 58.4 years, and had mean time since menopause of 11.2 years. At the lumbar spine, mean baseline BMD T-scores ranged from -1.48 to -1.39 in all the active treatment groups and was -1.52 in the placebo group. At the total hip, mean baseline BMD T-scores ranged from -0.82 to -0.73 in all the active treatment groups and was -0.90 in the placebo group.

In substudy II, a total of 431 subjects were randomized and took study product for the four groups of interest; (b) (4) to the BZA 20 mg/ CE 0.625 mg group, 111 to the BZA 20 mg/ CE 0.45 mg group, 107 to the Raloxifene group, and 108 to the placebo group. For the primary efficacy endpoint, 393 of the 431 randomized subjects were included in the MITT analysis. For a sensitivity analysis of the primary efficacy endpoint, 22 subjects in the MITT population (which is 4% to 7% of the subjects across the four treatment groups) had missing source documentation and were excluded. The Clinical Reviewer concurred with this decision. The study results were not affected by the removal of these 22 subjects because analyses including all subjects gave similar results.

Table 3.2
Study 3115A1-303: Randomization and Disposition of Substudy II Subjects

	BZA 20 mg/ CE 0.625 mg	BZA 20 mg/ CE 0.45 mg	Raloxifene 60 mg	Placebo
Number Randomized and Took Study Product (ITT)	(b) (4)	111	107	108
Completed n (%)*		85 (76.6)	68 (63.6)	74 (68.5)
Discontinued n (%)*		26 (23.4)	39 (36.4)	34 (31.5)
Number in MITT Population, Lumbar Spine BMD		101 (91.0)	97 (90.6)	99 (91.7)
Number Without Missing Source Documentation (MITT)		95 (85.6)	90 (84.1)	95 (88.0)
Primary Reason for Discontinuation n (%)*:				
Adverse Event		5 (4.5)	15 (14.0)	16 (14.8)
Death		0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-up		4 (3.6)	7 (6.5)	2 (1.9)
Other		6 (5.4)	7 (6.5)	8 (7.4)
Protocol Deviation		2 (1.8)	1 (0.9)	2 (1.9)
Subject Withdrew Consent		8 (7.2)	8 (7.5)	5 (4.6)
Lack of efficacy		1 (0.9)	1 (0.9)	1 (0.9)

Source: Table 8-2, page 77, Study 3315A1-303 report and Statistical Reviewer's listing based on SAS datasets DS and SCE1-DS.

* With respect to number of randomized subjects who took study product.

Discontinuation rates ranged from 23.4% to 36.4% in the active treatment groups and the rate was 31.5% in the placebo group. The primary reasons for study discontinuation were adverse event (4.5% to 14.0% for active treatment and 14.8% for placebo), withdrawal of consent (7.2% to 8.6% for active treatment and 4.6% for placebo), and other (5.4% to 6.5% for active treatment and 7.4% for placebo).

All groups in substudy II were similar in baseline and demographic characteristics based on the ITT population. The majority of subjects were Caucasian (>77%) and had a mean age of 52.1 years, and had mean time since menopause of 3.0 years. At the lumbar spine, mean baseline BMD T-scores ranged from -0.92 to -0.81 in all the active treatment groups and was -0.94 in the placebo group. At the total hip, mean baseline BMD T-scores ranged from -0.38 to -0.33 in all the active treatment groups and was -0.41 in the placebo group.

3.2.6 Study 3115A1-303 Results and Conclusions

The incidence of hyperplasia was acceptable (remained below 2%) at month 12 for all treatment groups except the BZA 10/CE 0.625 group and the BZA 10/CE 0.45 group (Appendix Table A1). Based on the hierarchical testing procedure for this first step (see Appendix), because there are significant results for four of the six treatment groups, testing can proceed to the next step to evaluate the BMD endpoint.

For the remainder of this review, only the BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg dose results are discussed because these are the doses sought for marketing. The Raloxifene 60 mg results are presented for use by the clinical reviewer but are not discussed here because they are not to be labeled. The results for the BZA 20 mg/CE 0.625 and BZA 20 mg/CE 0.45 mg dosages are made within the context of the overall testing procedure for each substudy (see section 3.2.2). Results for the other BZA/CE dosages in this study were also statistically significant at both the lumbar spine and total hip but are not reported because they are not the ones sought by the Applicant for marketing.

The Applicant's results, which I have verified, and the results when subjects with missing source documentation are excluded for the primary efficacy endpoint of percent change from baseline in lumbar spine BMD at Month 24 and important secondary efficacy endpoint of percent change from baseline in total hip BMD at Month 24 are presented in Tables 3.3 through 3.6 for each substudy (menopause subgroup). Analyses for the entire population are in Tables 3.3 and 3.5 while analyses excluding those subjects with missing source documentation are in Tables 3.4 and 3.6.

Both BZA/CE doses demonstrated improved efficacy compared to placebo at both the primary efficacy skeletal location of lumbar spine and the secondary important efficacy skeletal location of total hip as described below. Both analyses with and without those subjects with missing source documentation gave similar results.

Primary Endpoint: Lumbar Spine

For lumbar spine BMD:

- In the > 5 years since menopause subgroup, the mean percent change from baseline in lumbar spine BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 1.57% for BZA 20 mg/CE 0.45 mg vs. -1.51% for placebo. This gives a mean increase in lumbar spine BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 3.08% for BZA 20 mg/CE 0.45 mg compared to placebo (both $p < 0.001$).
- In the ≤ 5 years since menopause subgroup, the mean percent change from baseline in lumbar spine BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 1.69% for BZA 20 mg/CE 0.45 mg vs. -1.92% for placebo. This gives a mean increase in lumbar spine BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 3.61% for BZA 20 mg/CE 0.45 mg compared to placebo (both $p < 0.001$).

Table 3.3
Study 3115A1-303: Lumbar Spine BMD - Treatment Difference for Percent Change from Baseline at Month 24
(Primary Efficacy Population, LOCF)

	n	LS Mean*	LS Mean Difference from Placebo (95% C.I.)	p-value
> 5 Years Since Menopause				
				(b) (4)
BZA 20 mg/CE 0.45 mg	160	1.57%	3.08% (2.26%, 3.89%)	< 0.001
Raloxifene 60 mg	164	0.72%	2.23% (1.42%, 3.04%)	< 0.001
Placebo	159	-1.51%		
1 ≤ Years Since Menopause ≤ 5				
				(b) (4)
BZA 20 mg/CE 0.45 mg	101	1.69%	3.61% (2.64%, 4.57%)	< 0.001
Raloxifene 60 mg	97	0.15%	2.07% (1.09%, 3.05%)	< 0.001
Placebo	99	-1.92%		

Source: Statistical Reviewer's analysis and Tables 9-10 and 9-11, page 114, Study 3115A1-303 report.

Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; LOCF = last observation carried forward

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

For lumbar spine BMD when subjects with missing source documentation are excluded:

- In the > 5 years since menopause subgroup, the mean percent change from baseline in lumbar spine BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 1.64% for BZA 20 mg/CE 0.45 mg vs. -1.47% for placebo. This gives a mean increase in lumbar spine BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 3.11% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).
- In the ≤ 5 years since menopause subgroup, the mean percent change from baseline in lumbar spine BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 1.72% for BZA 20 mg/CE 0.45 mg vs. -1.90% for placebo. This gives a mean increase in lumbar spine BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 3.62% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).

Table 3.4
Study 3115A1-303: Lumbar Spine BMD - Treatment Difference for Percent Change from Baseline at Month 24
(Primary Efficacy Population Excluding Subjects with Missing Source Documentation, LOCF)

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

Source: Statistical Reviewer's analysis.

Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; LOCF = last observation carried forward

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

Important Secondary Endpoint: Total Hip

For total hip BMD:

- In the > 5 years since menopause subgroup, the mean percent change from baseline in total hip BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 1.06% for BZA 20 mg/CE 0.45 mg vs. -0.65% for placebo. This gives a mean increase in total hip BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 1.71% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).
- In the ≤ 5 years since menopause subgroup, the mean percent change from baseline in total hip BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 0.46% for BZA 20 mg/CE 0.45 mg vs. -1.41% for placebo. This gives a mean increase in total hip BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 1.87% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).

Table 3.5
Study 3115A1-303: Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 24
(Primary Efficacy Population, LOCF)

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

Source: Statistical Reviewer's analysis and Tables 9-12 and 9-13, page 118, Study 3115A1-303 report.

Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; LOCF = last observation carried forward

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

For total hip BMD when subjects with missing source documentation are excluded:

- In the > 5 years since menopause subgroup, the mean percent change from baseline in total hip BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 1.07% for BZA 20 mg/CE 0.45 mg vs. -0.65% for placebo. This gives a mean increase in total hip BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 1.73% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).
- In the ≤ 5 years since menopause subgroup, the mean percent change from baseline in total hip BMD at Month 24 was (b) (4) for BZA 20 mg/CE 0.625 mg and 0.55% for BZA 20 mg/CE 0.45 mg vs. -1.42% for placebo. This gives a mean increase in total hip BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 1.96% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).

Table 3.6
Study 3115A1-303: Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 24
(Primary Efficacy Population Excluding Subjects with Missing Source Documentation, LOCF)

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

Source: Statistical Reviewer's analysis.

Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; LOCF = last observation carried forward

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

3.2.7 Study 3115A1-3307 Subject Disposition and Baseline Characteristics

For study 3115A1-3307, overall, a total of 1886 subjects were randomly assigned to five treatment groups with 602 subjects included in the osteoporosis substudy.

Overall, 1843 subjects took at least 1 dose of test article. In this substudy, a total of 590 subjects were randomized to and took study product; ^{(b) (4)} subjects to the BZA 20 mg/ CE 0.625 mg group, 135 to the BZA 20 mg/ CE 0.45 mg group, 73 to the BZA 20 mg group, 70 to the MPA 1.5 mg/ CE 0.45 mg group, and 158 to the placebo group. For the primary efficacy endpoint, 512 of the 590 randomized subjects were included in the MITT analysis. Table 3.7 presents the number of randomized subjects and their disposition for this substudy.

Discontinuation rates ranged from 14.1% to 27.1% in all the active treatment groups and the rate was 18.4% in the placebo group. The primary reasons for study discontinuation were adverse event (5.8% to 11.4% for active treatment and 5.7% for placebo) and withdrawal of consent (0.0% to 6.7% for active treatment and 4.4% for placebo).

Table 3.7
Study 3115A1-3307: Randomization and Disposition of Osteoporosis Substudy Subjects

	BZA 20 mg/ CE 0.625 mg	BZA 20 mg/ CE 0.45 mg	BZA 20 mg	MPA 1.5 mg/ CE 0.45 mg	Placebo
Number Randomized and Took Study Product (ITT)	^{(b) (4)}	135	73	70	158
Completed n (%)*		109 (80.7)	55 (75.3)	51 (72.9)	129 (81.6)
Discontinued n (%)*		26 (19.3)	18 (24.7)	19 (27.1)	29 (18.4)
Number in MITT Population, Lumbar Spine BMD		119 (88.1)	56 (76.7)	59 (84.3)	139 (88.0)
Primary Reason for Discontinuation n (%)*:					
Adverse Event		10 (7.4)	7 (9.6)	8 (11.4)	9 (5.7)
Lost to Follow-up		1 (0.7)	3 (4.1)	3 (4.3)	0 (0.0)
Other		3 (2.2)	2 (2.7)	0 (0.0)	6 (3.8)
Protocol Deviation		2 (1.5)	2 (2.7)	4 (5.7)	4 (2.5)
Subject Withdrew Consent		9 (6.7)	0 (0.0)	2 (2.9)	7 (4.4)
Lack of efficacy		1 (0.7)	4 (5.5)	2 (2.9)	3 (1.9)

Source: Tables 8-1 and 8-3, pages 60 and 65, Study 3115A1-3307 report.

* With respect to number of randomized subjects who took study product.

All groups were similar in baseline and demographic characteristics based on the ITT population. The majority of subjects were Caucasian (>88.5%) and had a mean age of 52.9 years, had mean time since menopause of 2.5 years, and had a similar baseline mean BMD T-score of -0.90 at the lumbar spine.

3.2.8 Study 3115A1-3307 Results and Conclusions

For the remainder of this review, only the BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg dose results are discussed because these are the doses sought for marketing. The BZA 20 mg and MPA 1.5 mg/CE 0.45 mg results are presented for use by the clinical reviewer but are not discussed here because they are not to be labeled.

The Applicant's results, which I have verified, for the primary efficacy endpoint of percent change from baseline in lumbar spine BMD at Month 12 and important secondary efficacy endpoint of percent change from baseline in total hip BMD at Month 24 are presented in Tables 3.8 and 3.9 for women less than 5 years since menopause. Both BZA/CE doses demonstrated improved efficacy compared to placebo at both the primary efficacy skeletal location of lumbar spine and the secondary important efficacy skeletal location of total hip as described below. The BZA 20 mg and MPA 1.5 mg/ CE 0.45 mg results are presented for use by the clinical reviewer but are not to be labeled.

Primary Endpoint: Lumbar Spine

For lumbar spine BMD:

- In women < 5 years since menopause, the mean percent change from baseline in lumbar spine BMD at Month 12 was (b) (4) for BZA 20 mg/CE 0.625 mg and 0.24% for BZA 20 mg/CE 0.45 mg vs. -1.28% for placebo. This gives a mean increase in lumbar spine BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 1.51% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).

Table 3.8
Study 3115A1-3307: Lumbar Spine BMD - Treatment Difference for Percent Change from Baseline at Month 12
(Primary Efficacy Population, LOCF)

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

Source: Statistical Reviewer's analysis and Table 9-4, page 101, Study 3115A1-3307 report.

Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; LOCF = last observation carried forward

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

Important Secondary Endpoint: Total Hip

For total hip BMD:

- In women < 5 years since menopause, the mean percent change from baseline in total hip BMD at Month 12 was (b) (4) for BZA 20 mg/CE 0.625 mg and 0.50% for BZA 20 mg/CE 0.45 mg vs. -0.72% for placebo. This gives a mean increase in total hip BMD of (b) (4) for BZA 20 mg/CE 0.625 mg and 1.21% for BZA 20 mg/CE 0.45 mg compared to placebo (both p < 0.001).

Table 3.9
Study 3115A1-3307: Total Hip BMD - Treatment Difference for Percent Change from Baseline at Month 12
(Primary Efficacy Population, LOCF)

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

Source: Statistical Reviewer's analysis and Tables 9-5, page 105, Study 3115A1-3307 report.

Abbreviations: BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate; LOCF = last observation carried forward

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

3.3 Evaluation of Safety

For information about the evaluation of safety, refer to the clinical evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

The clinical reviewer did not identify any additional subgroup populations of interest for statistical review.

5. CONCLUSIONS

5.1 Statistical Issues

There was one statistical analysis issue identified in this submission for the prevention of postmenopausal osteoporosis indication. During the pre-NDA process for this application, the Division learned of multiple problems with the availability/existence of source documents (see section 3.1). This issue affected study 3115A1-303 but not study 3115A1-3307. There were few subjects with missing source documents (range from 3% to 7%, see section 3.2.5). A sensitivity analysis of the efficacy data for lumbar spine BMD and total hip BMD that excluded those subjects with missing source documents did not appreciably affect the results in study 3115A1-303 (see section 3.2.6).

Otherwise, the Applicant adhered to statistical methods for the primary and important secondary endpoints as specified in the protocol and Statistical Analysis Plan.

5.2 Collective Evidence

The two submitted studies provide supportive evidence demonstrating the efficacy of two dosages of bazedoxifene/conjugated estrogens (BZA/CE) for the prevention of osteoporosis in postmenopausal women based on lumbar spine bone mineral density (primary endpoint) and total hip bone mineral density (important secondary endpoint). Overall, there was an increase in the bone mineral density (BMD) of the lumbar spine and total hip with BZA/CE use compared to placebo.

The evidence is based on the results of comparisons between BZA/CE and placebo with respect to percent change from baseline after treatment in: 1) lumbar spine BMD and 2) total hip BMD from two multinational, randomized, multicenter, double-blind, parallel-group, placebo- and active-controlled studies. The focus is on women who were no more than 5 years postmenopausal.

For the primary endpoint, compared to placebo, both BZA/CE dosages increased the mean percent change from baseline in lumbar spine BMD by (b) (4) for BZA 20 mg/CE 0.625 mg and by 3.6% for BZA 20 mg/CE 0.45 mg

in one study after 2 years of treatment and by (b) (4) for BZA 20 mg/CE 0.625 mg and by 1.5% for BZA 20 mg/CE 0.45 mg in the second study after 1 year of treatment.

For the important secondary endpoint, compared to placebo, both BZA/CE dosages increased the mean percent change from baseline in total hip BMD by (b) (4) for BZA 20 mg/CE 0.625 mg and by 1.9% for BZA 20 mg/CE 0.45 mg in one study after 2 years of treatment and by (b) (4) for BZA 20 mg/CE 0.625 mg and by 1.2% for BZA 20 mg/CE 0.45 mg in the second study after 1 year of treatment.

From a statistical perspective, the two submitted studies (2-year Study 3115A1-303 and 1-year Study 3115A1-3307) provide supportive evidence demonstrating the efficacy of (b) (4) BZA 20 mg/CE 0.45 mg for the prevention of osteoporosis in postmenopausal women based on the endpoints lumbar spine bone mineral density and total hip bone mineral density. Overall, there was an increase in the bone mineral density of the lumbar spine and total hip with both dosages of BZA/CE use compared to placebo.

5.3 Conclusions and Recommendations

The two submitted studies provide supportive evidence demonstrating the efficacy of (b) (4) (b) (4) BZA 20 mg/CE 0.45 mg for the prevention of osteoporosis in postmenopausal women.

5.4 Labeling Recommendations

There are no major areas of disagreement with the Applicant's proposed labeling from a statistical perspective.

For both studies, the primary and key secondary efficacy results are very similar between the analyses that include subjects with missing source documents and those that exclude subjects with missing source documents. Therefore, for both the primary and important secondary efficacy results, I recommend using the results from the analyses that exclude subjects with missing source documents because the data can only be verified for those subjects with source documents. These results are found in the following tables: Tables 3.4 and 3.6 for study 3115A1-303 and Tables 3.8 and 3.9 for study 3115A1-3307.

APPENDIX

For the analysis of hyperplasia, the Agency requested that when 3 pathologists gave disparate readings, the most severe reading was assigned as the diagnosis rather than the majority opinion.

For the primary analysis of incidence of hyperplasia at month 12, the 1-sided CIs for the BZA/CE treatment groups were tested in a stepwise manner to control the overall type I error rate due to multiple evaluations (6 doses). In the first step, 2 dose groups (40 mg and 20 mg BZA with CE 0.45 mg) were tested simultaneously, and to adjust for the dual comparisons the 97.5% 1-sided CIs were used rather than the 95% CIs.

BZA 40 mg/CE 0.45 mg (Regimen 6), and
 BZA 20 mg/CE 0.45 mg (Regimen 5)
 ↓
 BZA 10 mg/CE 0.45 mg (Regimen 4)

If neither Regimen 6 nor Regimen 5 was found to have an acceptable incidence of hyperplasia, then the analysis was considered completed and the rates for all 6 dose regimens were considered not acceptable. If the incidence for either Regimen 6 or Regimen 5 was found acceptable using the 97.5% CI, then Regimen 4 was tested using the 95% CI. In addition, if the rates observed for either Regimen 6 or Regimen 5 was acceptable, then the 95% 1-sided CIs for the 3 regimens with 0.625 mg CE were tested individually in a stepwise manner as shown below. At each step, if the incidence of hyperplasia was found to be not acceptable then the analysis was considered complete and the rates for that regimen and all subsequent regimens were declared not acceptable.

BZA 40 mg/CE 0.625 mg (Regimen 3)
 ↓
 BZA 20 mg/CE 0.625 mg (Regimen 2)
 ↓
 BZA 10 mg/CE 0.625 mg (Regimen 1)

Table A1
Study 3115A1-303: Incidence of Endometrial Hyperplasia at Month 12
Alternate Definition of Hyperplasia* (Efficacy Evaluable Population)

	N	n	Incidence of Hyperplasia (%)	1-sided 95% CI
BZA 40 mg/CE 0.45	309	0	0.00	(0.00, 0.96)
BZA 20 mg/CE 0.45	335	0	0.00	(0.00, 0.89)
BZA 10 mg/CE 0.45	320	4	1.25	(0.43, 2.84)
(b) (4)				
Raloxifene 60 mg	298	0	0.00	(0.00, 1.00)
Placebo	312	0	0.00	(0.00, 0.96)

Source: Table 9-5, page 108, Study 3115A1-303 report

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

N = number of subjects with biopsies available at month 12 plus all subjects with hyperplasia prior to month 12

Abbreviation: CI =confidence interval

* Alternate definition of hyperplasia was requested by the FDA. In this definition, when 3 pathologists gave disparate readings, the most severe reading was assigned as the diagnosis rather than the majority opinion,

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/s/

SONIA CASTILLO
06/04/2013

MAHBOOB SOBHAN
06/04/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 22247 / Supporting Doc. 001 **Applicant:** Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc. **Stamp Date:** 9-26-2012 (receipt date of 10-3-2012)

Drug Name: bazedoxifene acetate/conjugated estrogens (BZA/CE) **BLA Type:** Standard

Indication: Treatment of vasomotor symptoms (VMS) and vulvar and vaginal atrophy (VVA) in postmenopausal women, and the prevention of postmenopausal osteoporosis.

This filing checklist is for the treatment of postmenopausal osteoporosis portion of the indication sought by the Applicant. The three studies pertinent to this portion of the indication are summarized in the table below.

Brief Summary of Clinical Studies for BZA/CE

Study Number (Country) Dates of Study Conduct	Subject Population	Treatment	ITT ^{1,2} Population	Design ³
3115A1-303-US/EU/BR (Belgium, Brazil, Finland, Italy, Netherlands, Norway, Poland, Spain, United States) April 2002 to January 2006	Healthy, postmenopausal women with uterus	BZA 10 mg/CE 0.45 mg BZA 20 mg/CE 0.45 mg BZA 40 mg/CE 0.45 mg (b) (4) Raloxifene 60 mg Placebo Total ³	290 293 284 (b) (4) 295 292 2315	DB, R, PC, PG, MC, MN, 2-year
3115A1-3307-WW (Argentina, Australia, Chile, Colombia, Denmark, Finland, Hungary, New Zealand, Norway, Poland, United States) January 2009 to February 2011	Healthy, postmenopausal women with uterus	BZA 20 mg/CE 0.45 mg (b) (4) CE 0.45 mg/MPA 1.5 mg BZA 20 mg Placebo Total	135 (b) (4) 70 73 158 590	DB, R, PC, PG, MC, MN, 1-year
3115A1-304-WW (United States) October 2005 to August 2008	Healthy, postmenopausal women with uterus	BZA 20 mg/CE 0.45 mg (b) (4) CE 0.45 mg/MPA 1.5 mg Placebo Total	177 (b) (4) 88 84 527	DB, R, PC, PG, MC, MN, 1-year

Source: Statistical Reviewer's listing.

¹ ITT = Intent to Treat, received investigational product

² The number of subjects for each study refer only to those who were part of the osteoporosis prevention substudy.

³ DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter, MN = Multinational

On **initial** overview of the NDA application for Refuse-To-File (RTF):

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission			X	
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			X	All subjects were women with mean age greater than 56 years.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Program files are present; SAS can open data sets

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE Yes

STATISTICS FILING CHECKLIST FOR A NEW NDA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses were pre-specified in protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			The interim analyses were pre-specified and described in the protocol but the charter with full details was not included. See requests below.
Appropriate references for novel statistical methodology are included.			X	
Safety data organized to permit analyses across clinical trials in the BLA.			X	Safety data format and coding issues addressed by the clinical team; a clinical information request has been sent to the Applicant to resubmit safety datasets in correct form prior to filing date.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Requests to the Applicant for the 74-day letter: There are no requests for the 74-day letter.

Requests for information that are not hold issues:

The following three requests were conveyed to the Applicant on November 19, 2012:

- Study 3115A1-3307-WW: Either provide the location within the application or submit to the application the interim analysis charter. An interim analysis was cited in the statistical analysis plan (dated 11-23-2010 on page 11 of the SAP or page 13 of 126 of section 16.1.9) and in protocol amendment 2 (dated June 8, 2010 on page 64 of the protocol or page 232 of 255 of section 16.1.1).
- 3115A1-303-US/EU/BR: Either provide the location within the application or submit to the application the interim analysis charter for the interim analysis that was carried out.
- Provide the location within the application or submit to the application the interim analysis charter for any interim analyses that were carried out for all pivotal studies submitted to the application.

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/s/

SONIA CASTILLO
11/21/2012

MAHBOOB SOBHAN
11/21/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 022-247/000 **Applicant:** Wyeth

Stamp Date: 10/03/2012

Drug Name: bazedoxifene/conjugated estrogens

NDA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		Women only study
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Internal Comments for this NDA:



(b) (5)

Kate Dwyer, Ph.D.	11/20/12
Reviewing Statistician	Date
Mahboob Sobhan, Ph.D.	11/20/12
Supervisor/Team Leader	Date

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/s/

KATE L DWYER
11/21/2012

MAHBOOB SOBHAN
11/21/2012