CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-674

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-674

Drug Name: Menostar (estradiol transdermal system)
Indication(s): Prevention of postmenopausal osteoporosis (PMO)
Applicant: Berlex
Date(s): Submitted August 8, 2003
User fee goal date June 8, 2004
Review Priority: Standard 10-month cycle

Biometrics Division: HFD-715
Statistical Reviewer: J. Todd Sahlroot, Ph.D.
Team Leader, DB2

Medical Division: HFD-510
Clinical Team: Bruce Stadel, M.D.
Eric Colman, M.D.
Project Manager: Pat Madara

Keywords: NDA review, clinical studies

Introduction

The primary statistical review of this NDA was performed by Dr. Japo Choudhury (HFD-715). His review discusses study design and analysis results for Study 98188, a randomized, multicenter, Phase 3 trial comparing Menostar to placebo on spine and hip BMD.

This abbreviated review is not intended as a comprehensive examination of the data but focuses instead on two specific issues in greater detail: (1) sensitivity analyses conducted by the sponsor intended to address the robustness of the primary analysis with respect to missing data, and (2) subgroup analyses of the data defined by baseline estradiol (E2) level:

- Issue 1. The sponsor's primary analyses of spine and hip BMD data at 24 months were statistically significant ($p<.001$) and used 90% of the 417 randomized patients. While 90% is a relatively high percentage of patients, it is important to confirm the primary analysis results since Menostar 1mg (3.25 cm^2 transdermal patch) used an ultra low dose equal to half the lowest approved dose for PMO. This reviewer will examine the sponsor's sensitivity analyses of spine and hip BMD data to address the issue of the robustness of the primary analyses with respect to missing data.

- Issue 2. The reviewing Medical Officer, Dr. Bruce Stadel, noted differences in response for spine and hip BMD between subgroups defined by baseline estradiol (E2) level. To assess whether the observed treatment effects in the subgroups differed statistically, this reviewer conducted tests for interaction between treatment group (menostar, placebo) and baseline E2 level (< 5 pg/ml, ≥ 5 pg/ml) for both BMD endpoints.

Sensitivity analyses

Four hundred seventeen (417) patients were randomized to Menostar (n=208) or placebo (n=209). Of this total, 375 (90%) patients contributed data to the sponsor's primary analysis of spine BMD data at 24 months. 374 (90%) patients contributed data to the sponsor's primary analysis of hip BMD data at 24 months. The sponsor referred to these results as the "full analysis set".

BMD data were to be collected at 12 and 24 months, and at the end-of-study visit if the patient discontinued prematurely.

The sponsor conducted two sensitivity analyses of spine and hip BMD. These analyses used on-study data for completers and imputed values for non-completers. Sensitivity analysis #1 used all randomized patients (n=417) and imputed the placebo mean for non-completers in both treatment groups. Sensitivity analysis #2 imputed means from the opposite treatment group for non-

completers. This analysis used 394 patients. In each case, the standard error of the treatment difference and degrees of freedom were obtained from completers.

The sponsor did not elaborate on why the two analyses used different numbers of patients.

Both imputation procedures are conservative. Imputation procedure #2 is the more conservative of the two.

Table 1 shows treatment differences for % change from baseline in lumbar spine and hip BMD at 24 months. The sensitivity analyses gave nearly identical results. Each produced a smaller effect size than the full analysis set. The statistical results were still highly significant (p<.001). In this reviewer's opinion, the sensitivity analyses provide convincing evidence to support the results obtained under the full analysis set.

Table 1. Lumbar spine and hip BMD % change from baseline at 24 months [1]

Analysis set	Treatment difference	
	Spine	hip
"full analysis set"	(n=375)	(n=374)
Observed mean difference	2.45	1.55
SE [2]	0.39	0.32
p-value	p<.001	p<.001
Sensitivity analysis #1 [3]	(n=417)	(n=417)
Observed mean difference	2.22	1.41
SE [2]	0.39	0.31
p-value	p<.001	p<.001
Sensitivity analysis #2 [3]	(n=394)	(n=393)
Observed mean difference	2.22	1.41
SE [2]	0.39	0.31
p-value	p<.001	p<.001

1 The Table shows results for treatment differences only, not by treatment group. The SAS output provided by the sponsor indicated treatment differences only.
2 SE for treatment difference from ANCOVA model with effects for treatment, center and baseline BMD as covariate
3 Sensitivity analysis #1 imputed the placebo mean for non-completers. Sensitivity analysis #2 imputed the opposite treatment mean for non-completers

Subgroup analyses by estradiol level

E2 was measured as a continuous variable. See Dr. Stadel's review for a justification of the 5 pg/ml cut point to define E2 subgroups. To assess whether the observed treatment effects in the subgroups were statistically different, this reviewer conducted tests for interaction between treatment group (Menostar,

placebo) and baseline E2 level (< 5 pg/ml, ≥ 5 pg/ml) for spine BMD, the primary endpoint, and hip BMD, a secondary endpoint.

Table 2 shows data summaries for the hip and spine BMD endpoints by E2 level. These data match the entries in Table 6 of Dr. Stadel's review. For both hip and spine, Menostar increased BMD relative to placebo in each subgroup. However, treatment differences in the low E2 subgroup were at least double treatment differences in the high E2 subgroup. The interaction was nominally significant on the primary endpoint (p=0.039). For hip BMD, the interaction was marginally significant (p=0.056). Because treatment differences in each subgroup had the same sign, the interactions are considered quantitative in nature rather than qualitative.

Table 2. Spine and hip % change in BMD from baseline at 24 months by estradiol (E2) subgroup [1]

Endpont Subgroup	Menostar	Placebo	Treatment Difference	p-value [2]
Mean % change in lumbar spine BMD from baseline				
E2 < 5 pg/ml	(n=101) 3.50	(n=97) 0.29	3.21	.039
E2 ≥ 5 pg/ml	(n=88) 2.40	(n=89) 0.81	1.59	
Mean % change in hip BMD from baseline				
E2 < 5 pg/ml	(n=101) 1.04	(n=96) -1.09	2.13	.056
E2 ≥ 5 pg/ml	(n=88) 0.61	(n=89) -0.31	0.92	

[1] Based on the sponsor's full analysis set (spine, n=375; hip, n=374).
[2] P-value from test for interaction between treatment group and E2 subgroup. The statistical model used effects for treatment, E2 subgroup and interaction.

Conclusions

The sponsor's sensitivity analyses of the spine and hip BMD data at 24 months confirm the primary results using the full analysis set.

The treatment-by-E2 interaction was nominally statistically significant for spine BMD (p=0.039). The interaction was marginally significant for hip BMD (p=0.056).

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

/s/

Todd Sahlroot
5/28/04 11:54:20 AM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-674/N_000
Name of drug:	Menostar™ (estradiol transdermal system)
Applicant:	Berlex Laboratories, Inc.
Indication:	Prevention of postmenopausal osteoporosis
Documents reviewed:	Location of the NDA in EDR (electronic documents room): \\CDSESUB1\N21674\2003-08-07\clinstat and others in \\CDSESUB1\N21674\
Project manager:	Patricia Madara (HFD-510)
Clinical reviewer:	Bruce Stadel, M.D. (HFD-510)
Dates:	8/7/03; user fee date – 6/8/04
Statistical reviewer:	Japobrata Choudhury, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Concurrence by:	Stephen Wilson, Dr.P.H. (HFD-715)
Keywords:	NDA review, clinical studies

Contents

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

This study has provided statistical evidence in favor of the efficacy of ultra-low dose estradiol in the prevention of osteoporosis in postmenopausal women with intact uteri when administered using a transdermal patch placed on the lower abdomen and replaced weekly.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Note: New Drug Application is abbreviated by NDA. Except where specifically mentioned otherwise (as notes, reviewer's comments, conclusions, etc.), all other results and statements in this document are the sponsor's. In particular, the material in Sections 2.1 to 2.3.2 is almost verbatim from the sponsor's submission. Elsewhere, the sponsor's statements may be slightly changed for brevity or for clarity.

Berlex markets estradiol transdermal system (Climara®) in six approved patch sizes ranging from 25 cm (estradiol daily delivery rate of 100 micrograms/day) down to 6.5 cm (25 micrograms estradiol/day). All six sizes are approved for the indications relief of vasomotor symptoms and prevention of postmenopausal osteoporosis. Menostar™, the product for which this application is being submitted, is identical in composition to Climara® in that it is cut from the same rollstock as are all six marketed patches. Menostar™ is simply cut to be half the size of the lowest Climara® strength. Only the prevention of osteoporosis indication is being sought for Menostar™. In support of this indication, the sponsor has provided results from the following study (Study 98188), whose synopsis is provided in Section 2.1 Introduction and Background:

A11926 (98188)	Barbier S (All study centers were located in the United States.) NA	01/2000 24 months (26 cycles) Completed	Double-blind, randomized, placebo-controlled, parallel-group multicenter Phase 3	1.0 mg E2 transdermal system (3.25 cm^2) Placebo transdermal system (3.25 cm^2)	208 209	60-80 (66.8) 60-80 (66.7) 417 Females 385 Caucasians 8 Blacks 13 Asians 3 Hispanics or Latinos 3 Hawaiians or Other Pacific Islanders 5 Other	1) a11926.pdf 2) NA 3) define.pdf 4) crftoc.pdf

1.3 PRINCIPAL FINDINGS

This study has provided statistical evidence in favor of the efficacy of Ultra-low estradiol in the prevention of osteoporosis in postmenopausal women with intact uteri when administered using a transdermal patch placed on the lower abdomen and replaced weekly.

More detailed discussions are in the Section 2.3.3.1.5 Efficacy Results (Sponsor's Analyses). There were no exceptionally striking findings.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Specific Indication: Prevention of postmenopausal osteoporosis in women with or without a uterus.

Name of finished product: Estradiol Transdermal System

Name of active ingredient: 17ß- Estradiol

Title of study (Study 98188): A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of an Ultra-low Dose of Estradiol Given by Continuous Transdermal Administration in the Prevention of Osteoporosis in Postmenopausal Women

Investigator(s): Nine investigators participated in this trial. A complete list of investigators is provided in Appendix 16.1.4.

Study period (years) date of first enrollment: 10 Jan 2000
date of last completion: 23 Nov 2002
Clinical phase: 3

Objectives: Primary: The primary efficacy objective was to demonstrate the superiority of using an ultra-low dose of unopposed estradiol, administered transdermally, compared with placebo, in the prevention of osteoporosis in postmenopausal women with intact uteri. The primary safety objective was to demonstrate the endometrial safety of an unopposed estradiol patch compared with placebo in postmenopausal women.

Secondary: The following were the secondary objectives: • To evaluate the effects of unopposed estradiol transdermal treatment on bone density of the total hip. • To evaluate the effects of unopposed estradiol transdermal treatment on variables of biochemical markers of bone metabolism (serum osteocalcin, serum carboxyterminal telopeptide of type I collagen [ICTP], serum bonespecific alkaline phosphatase, and urinary. deoxypyridinoline/ creatinine ratio). • To evaluate the effect of unopposed estradiol transdermal compared with placebo on the well being of postmenopausal women. • To evaluate the effect of unopposed estradiol compared with placebo on cognitive function.

Methodology: BMD was measured by dual-energy x-ray absorptiometry (DXA). In addition, biochemical markers of bone metabolism were evaluated. Endometrial hyperplasia was evaluated by endometrial biopsy.

General safety was evaluated by recording and evaluating adverse events, and monitoring changes in physical examinations (including vital signs), and clinical laboratory results.

Total number of patients Planned: Approximately 410 postmenopausal women with intact uteri

Total number of patients Analyzed: 417 (safety set and full analysis set); 367 (per protocol set)

Diagnosis and main criteria for inclusion: Postmenopausal women, ≥ 60 and ≤ 80 years old with an intact uterus, negative endometrial biopsy, ≥ 5 years after menopause, evaluable BMD of spine and hip. If inadequate tissue following endometrial biopsy, patients must have endometrial thickness < 4 mm on transvaginal ultrasound.

Mode of administration: Transdermal delivery system

Duration of treatment: 24 months (26 cycles of 28-day duration per cycle)

Test product: 1.0 mg of 17ß- Estradiol in a transdermal system Dose: One 3.25 cm^2 patch containing 1.0 mg estradiol was worn per week. The estradiol delivery rate was 0.014 mg per day.

Reference therapy: Placebo Dose: One 3.25 cm2 patch was worn per week.

Additional Medication: TUMS® tablet (400 mg of calcium each) and Centrum® tablet (162 mg of calcium each). The patients were also provided with vitamin D supplements (400 IU).

Criteria for evaluation: Efficacy: Efficacy was primarily evaluated by calculating percent change from baseline in BMD as measured by DXA for the Month 24 endpoint for the lumbar spine (AP view, L2- L4). Percent change from baseline in BMD at the 12- month

endpoint for the lumbar spine (AP view, L2- L4) was also compared between treatment groups, as was change and percent change in BMD for the total hip.

Also evaluated were: • Changes in biochemical markers of bone metabolism (serum osteocalcin, bone specific alkaline phosphatase, carboxyterminal telopeptide of type 1 collagen (ICTP), and the urinary deoxypyridinoline/ creatinine ratio). • The well- being of postmenopausal women as assessed by the Profiles of Mood States (POMS); The Medical Outcomes Study 36- Item Health Survey (SF- 36), Depression Survey CES-D10, urinary health and sexual function questionnaires, and • Cognitive function.

Safety: The effect on the endometrium, i.e., the incidence of endometrial hyperplasia, was the primary safety variable. Adverse event reports including fractures, bleeding and spotting, physical examinations findings, vital sign measurements, and clinical laboratory results were also evaluated.

2.2 DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room:

\\CDSESUB1\N21674\\2003-11-14\crt

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Note: The sponsor's results and conclusions are following. To re-emphasize, Sections 2.1 to 2.3.2 are almost verbatim from the sponsor's submission. This reviewer's findings have been presented at appropriate places. His silence in Sections 2.1 to 2.3.2 does not imply agreement with the sponsor's statements (his comments, if any, are in italic as notes).

Note: Statistical review and analyses have been done by the reviewer only with respect to the primary efficacy evaluations: "Change from baseline to 24 months in bone mineral density (BMD) measurement of the lumbar spine (AP view, L2-L4)."

Change and Percent Change From Baseline in BMD (g/cm2) for Lumbar Spine - Full Analysis Set

		Visit 3 Month 12	12-Month Endpoint[a]	Visit 6 Month 24	24-Month Endpoint[a]
		Change (%)	Change (%)	Change (%)	Change (%)
Ultra-low Estradiol (N = 208)	n	187	189	173	189
	Mean	0.021 (2.29)	0.021 (2.29)	0.028 (3.05)	0.027 (2.99)
	Median	0.020 (2.19)	0.020 (2.19)	0.031 (3.22)	0.030 (3.18)
	SD	0.029 (3.10)	0.029 (3.10)	0.036 (3.94)	0.036 (3.89)
	Minimum	-0.062 (-6.72)	-0.062 (-6.72)	-0.080 (-6.38)	-0.080 (-6.72)
	Maximum	0.096 (10.30)	0.096 (10.30)	0.142 (20.12)	0.142 (20.12)
Placebo (N = 209)	n	182	186	160	186
	Mean	0.005 (0.58)	0.005 (0.51)	0.007 (0.74)	0.005 (0.54)
	Median	0.003 (0.27)	0.002 (0.16)	0.005 (0.47)	0.005 (0.40)
	SD	0.030 (3.23)	0.030 (3.25)	0.033 (3.60)	0.034 (3.69)
	Minimum	-0.082 (-9.36)	-0.082 (-9.36)	-0.074 (-8.37)	-0.082 (-9.36)
	Maximum	0.094 (11.89)	0.094 (11.89)	0.120 (13.16)	0.120 (13.16)
	p-value[b]		<0.001		<0.001

N = total number of patients; n = number of patients with data available; SD = standard deviation.
[a] Represents the last observed postbaseline value (at that time point) carried forward.
[b] P- values are for between-treatment group comparisons of percent change from baseline. Default ANCOVA model has terms for treatment, center, and baseline as a covariate.
Reference: Table 16

Reviewer's Note: From the referenced Table 16, the p-value is <0.001 for both "change" and "percent change" from baseline.

The mean values at baseline were not statistically (p = 0.054) different between the treatment groups, however the ultra-low estradiol patients had a lower mean BMD value (0.936 g/ cm^2) at baseline than did placebo patients (0.955 g/cm^2).

Ultra-low estradiol patients demonstrated a statistically significantly ($p < 0.001$) greater mean percent change from baseline for lumbar spine BMD compared with placebo patients for both the 12- and 24-month endpoints. Mean percent increases for ultra-low estradiol patients were 2.29% and 2.99% at the 12- and 24-month endpoints, respectively, and were 0.51% and 0.54% for placebo patients at the same time points. Therefore, ultra-low estradiol patients experienced a more than 4-fold greater proportional increase (2.29/0.51 = 4.5 and 3.00/0.54 = 5.5) for BMD in their lumbar spine than placebo patients at both the 12-and 24-month endpoints, as demonstrated by percent change from baseline.

Sponsor's Discussion and Overall Conclusions

Estrogen deficiency is characterized by vasomotor symptoms (particularly hot flushes and sweating), genitourinary atrophy, and a decrease in bone mineral density. This is particularly true following menopause, when bone loss occurs at an accelerated rate. Estrogen therapy is recognized for the treatment of climacteric symptoms and the

prevention of postmenopausal osteoporosis, has beneficial effects on skin and hair, has been reported to improve quality of life and well- being of postmenopausal women. However, since estrogens may cause proliferation of the endometrium, long- term unopposed administration of estrogens may have local adverse effects on the uterus, e.g., endometrial hyperplasia or cancer. Therefore, it is important that the lowest effective dose of estrogen be used. With age, women are no longer willing to accept vaginal bleeding. Therefore, the ideal intervention with estradiol would be to use an efficacious dose that achieves adequate endometrial safety and a high rate of amenorrhea.

The objective of the present study was to demonstrate that an unopposed ultra- low dose (1 mg delivered transdermally continuously over a week at a rate of 0.014 mg per day) estradiol was superior to placebo in the prevention of osteoporosis in postmenopausal women.

The patients randomized to this study were mostly white women 60 years old and older, more than 80% of whom had T-scores at baseline > -2.5, and more than 90% had been pregnant at least once. Additionally, they all had intact uteri at study entry and were at least 5 years postmenopausal. The majority (> 90%) were nonsmokers and more than 40% of them reported consuming alcohol infrequently. There were no meaningful differences in baseline characteristics between the treatment groups at baseline.

Superiority of ultra-low estradiol was demonstrated by a statistically significantly ($p < 0.001$) greater mean percent increase from baseline in BMD of the lumbar spine for ultra-low estradiol patients compared with placebo patients for the 24-month endpoint - the primary measure of efficacy. In addition, compared with placebo patients, ultra-low estradiol patients demonstrated a greater mean percent increase from baseline in BMD of the total hip for the 24-month endpoint – the secondary measure of efficacy. The ultra-low estradiol patients also had significantly ($p < 0.001$) greater mean percent increases from baseline in BMD of the lumbar spine and total hip compared with placebo patients for the 12-month endpoint. The results were similar for both the full analysis set and the per protocol analysis set.

Ultra-low estradiol patients demonstrated mean percent increases from baseline in BMD of the lumbar spine at the 12- and 24- month endpoints of approximately 2.3% and 3.0%, respectively. Placebo patients achieved mean percent increases from baseline of approximately 0.5% for both the 12- and 24- month endpoints. Mean percent increases from baseline for ultra-low estradiol patients for the total hip were 0.9% and 0.8% at the 12- and 24- month endpoints, respectively. Placebo patients demonstrated mean bone losses of – 0.22% and - 0.71 at the 12- and 24-month endpoints, respectively.

The substantial and clinically meaningful percent increases from baseline in BMD of both the lumbar spine and hip at the 12- and 24-month endpoints demonstrated by ultra-low estradiol patients are supported by the results obtained from monitoring the biochemical markers of bone metabolism. Both markers of bone formation, i.e., osteocalcin and bone-specific alkaline phosphatase were statistically significantly

decreased from baseline during the study period for ultra-low estradiol patients. For ultra-low estradiol patients the markers of bone resorption, i.e., ICTP and the urinary deoxypyridinoline/creatinine ratio either were statistically significantly decreased compared with placebo patients, as in the case of the urinary deoxypyridinoline/ creatinine ratio, or as in the case of ICTP, statistically significantly decreased during the first year and statistically significantly less increased during the second year compared with placebo patients. The overall pattern demonstrated reduced bone turnover in ultra-low estradiol patients at the 12- and 24-month endpoints, which supports the clinically important BMD results.

There were no deaths in the study and the dropout rate due to adverse events (and overall) was low. After 12 months, no hyperplasia was found in any treatment group. After 24 months, endometrial hyperplasia was diagnosed in 1 (0.5%) ultra-low estradiol patient. No endometrial cancer was diagnosed at any time in either treatment group. Overall, the endometrial biopsy data demonstrated endometrial safety of 24 months of unopposed treatment with the ultra-low dose estradiol patch.

Endometrial hyperplasia was observed in a 63-year old nulliparous woman, with no recent estrogen use and no abnormal gynecological history. The patient did not report genital bleeding during the study. The endometrial biopsy at baseline showed normal strips of benign surface. The 12-month endometrial biopsy showed inactive/ atrophic endometrium. The 24-month endometrial biopsy showed atypical hyperplasia, which was confirmed by 2 independent readers. There was no endometrial stroma present between the endometrial glands and there was no evidence of a malignancy in the final endometrial biopsy. Subsequently, the pathologist found no evidence of mitoses. The conclusion of the primary pathologist (at the central laboratory) was that the type of endometrial hyperplasia seen is very rare, unusual, and not a precursor of adenocarcinoma. This information can be found in Appendix 16.6. The patient was treated with medroxyprogesterone acetate 10 mg, twice daily, and the follow- up endometrial biopsy 3 months later showed focal ciliated cell metaplasia. Six months after that, a saline ultrasonography and an endometrial biopsy were performed and the results from both were normal.

During the 24 months of the study, the lowest proportion of ultra-low estradiol patients who experienced amenorrhea was 84%, which occurred during reference Days 361 to 450. The lowest proportion of placebo patients reporting amenorrhea was 88%, which also occurred during Days 361 to 450. The proportion of patients who reported amenorrhea at the endpoint (final reference period carried forward) was 89% and 96% for ultra-low estradiol and placebo patients, respectively.

All other safety examinations demonstrated that ultra-low estradiol was safe and well tolerated. The overall adverse event pattern was as expected for the patient population studied. The occurrence of typical hormone- related adverse events such as breast pain and vaginal hemorrhage was lower than expected for estrogen treatments with almost no difference between the ultra-low estradiol and placebo groups. The most frequently

observed adverse event in the ultra- low estradiol group was leukorrhea (vaginal discharge), which occurred in 22 (10.6%) ultra-low estradiol patients compared with 3 (1.4%) placebo patients.

Sponsor's Overall Conclusions:

Ultra-low estradiol is safe and effective in the prevention of osteoporosis in postmenopausal women with intact uteri when administered using a transdermal patch placed on the lower abdomen and replaced weekly. In addition, transdermally administered ultra-low estradiol does not cause significant endometrial stimulation. Therefore, there is no need to add progestin to prevent endometrial hyperplasia.

2.3.2 STATISTICAL METHODOLOGIES

The sponsor stated in the Data Analysis Plan (DAP) (submitted on 2003-11-14), "The 24 Month endpoint analysis of percent change from baseline in BMD of lumbar spine (AP view L2-L4) is the primary efficacy analysis. The analysis methods described in Section 2.13 *(Reviewer's Note: Section 2.3.3.1.5 Efficacy Results (Sponsor's Analyses) of this document)* for continuous variables will be used to compare the change and percent change from baseline in BMD lumbar spine and total hip at the 12 Month and 24 Month endpoints as defined in Section 2.12 *(Note: of the DAP)*.

In addition, the paired t-test will be used to compare the value of the response variable at each visit to the baseline value within each treatment group. Summary statistics for change from baseline and percent change from baseline will be provided for 12 Month and 24 Month observed data."

Note: See Section 2.3.3.1.5 Efficacy Results (Sponsor's Analyses) for more details.

Appears This Way
On Original

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Only one Phase III study under Protocol **98188** (U.S.) has been conducted for this indication.

*2.3.3.1 Study Under Protocol **98188** (U.S.)*

2.3.3.1.1 Primary Objectives

To evaluate the efficacy of treatment utilizing an ultralow dose of unopposed estradiol given transdermally compared to placebo, in the prevention of bone loss and osteoporosis of the lumbar spine in postmenopausal non-hysterectomized women.

To evaluate the effect of unopposed estradiol transdermal compared to placebo on endometrial histology and bleeding patterns in postmenopausal women.

2.3.3.1.2 Disposition of Patients

Of the 717 patients screened, 417 women (208 in the ultra-low estradiol group and 209 in the placebo group) were randomized and received at least 1 dose of study medication. Of these 417 patients, 376 (90%) completed the 24-month study.

A total of 191 (91.8%) of 208 ultra-low estradiol patients and 185 (88.5%) of 209 placebo patients completed the trial. Eighty-three (19.9%) patients discontinued study medication prematurely. Of the 83, 35 (16.8%) were ultra-low estradiol patients and 48 (23.0%) were placebo patients.

Forty-one (9.8%) of the 417 patients discontinued study medication prematurely and study participation. Of these, 17 (8.2%) of 208 and 24 (11.5%) of 209 discontinued in the ultra-low estradiol and placebo groups, respectively (see Appendix 16.2.1). In addition to the 41 patients who discontinued study medication and dropped from the study prematurely, 42 patients (18 ultra-low estradiol and 24 placebo patients) discontinued study medication, but remained in the study to completion (see Appendix 16.2.1).

The most common (20 [4.8%] patients) reason for premature discontinuation from the study was consent withdrawal. The proportion (14 [6.7%] of 209) of placebo patients who withdrew consent was twice the proportion (6 [2.9%] of 208) of ultra-low estradiol patients. The proportion of patients who discontinued due to an adverse event was similar between groups, 8 (3.8%) of 208 for ultra-low estradiol patients and 6 (2.9%) of 209 for placebo patients.

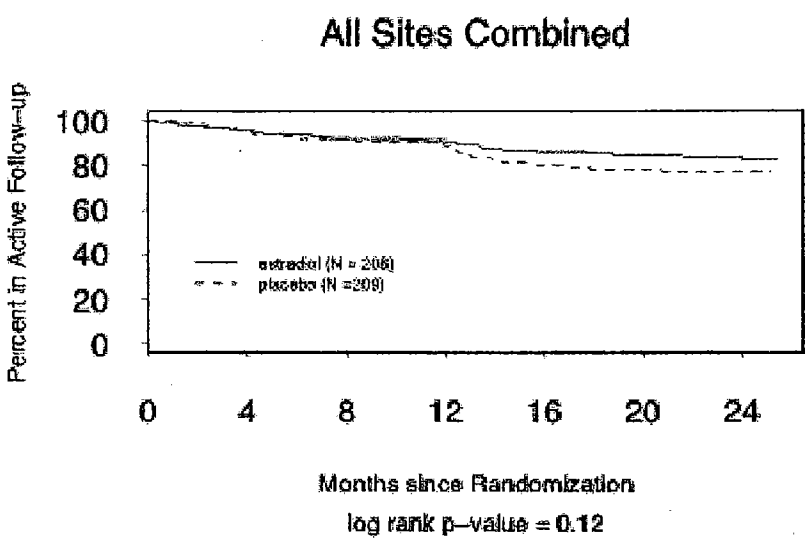
The number of patients screened, randomized, completed, and discontinued prematurely is presented by treatment group in Table below. Patient disposition by treatment group and visit are presented in Table 4 and by center and treatment group and visit in Table 5 (of the NDA).

Patient Disposition

	Treatment Groups		
Patient Disposition	**Ultra-low Estradiol**	**Placebo**	**Total**
Screened[a]	NA	NA	717
Randomized	208	209	417
Safety Set[b]	208	209	417
Full Analysis Set[c]	208	209	417
Completed Study n (%)	191 (91.8)	185 (88.5)	376 (90.2)
Prematurely Discontinued Study Medication n (%)	35 (16.8)	48 (23.0)	83 (19.9)
Prematurely Discontinued from Study n (%)	17 (8.2)	24 (11.5)	41 (9.8)
Adverse Event n (%)	8 (3.8)	6 (2.9)	14 (3.6)
Lack of Efficacy n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation n (%)	0 (0.0)	1 (0.5)	1 (0.2)
Withdrawal of Consent n (%)	6 (2.9)	14 (6.7)	20 (4.8)
Other[d] n (%)	3 (1.4)	3 (1.4)	6 (1.4)
Prematurely Discontinued Study Medication but Remained in Study n (%)	18 (8.7)	24 (11.5)	42 (10.1)
Treated with Study Medication for:			
>1 Months to ≤ 13 Months n (%)	185 (88.9)	185 (88.5)	370 (88.7)
>13 Months to ≤ 24 Months n (%)	173 (82.8)	161 (77.0)	334 (80.1)

NA = not applicable; n = number of patients.
a Only for patients in Screening Visit 1.
b All randomized patients who received at least 1 dose of study medication.
c All randomized patients who received at least 1 dose of study medication and had 1 postbaseline measurement.
d Other includes lost to follow-up patients. A patient withdrawn for more than 1 reason was counted once when determining number of withdrawals. Reference: Table 2 and Table 3

Percent of patients under active follow-up over time is presented below graphically:



Considering site-continuation rates (Statistical Appendix of the NDA), the rate was slightly imbalanced in the — site (between placebo and estradiol).

2.3.3.1.3 Demographic and Other Baseline Characteristics

The study population was predominantly white (92.3%); the mean ages were similar for both treatment groups, i.e., 66.8 and 66.7 years for ultra-low estradiol and placebo patients, respectively; mean weight at baseline was 73.5 kg for ultra-low estradiol patients, and 73.3 kg for placebo patients.

The majority (93%) of women enrolled in both treatment groups were nonsmokers. More than 40% of the women in both treatment groups reported either consuming alcohol only once or no alcohol being consumed in the preceding 30 days prior to screening (47.1% in the ultra-low estradiol group and 44.5% in the placebo group).

Mean reported calcium and vitamin D intake was 745.5 mg/ day for ultra-low estradiol patients and 691.1 mg/ day for placebo patients, or about 60% of the recommended daily requirement of 1200 mg/ day. There were no statistically significant differences in demographics or baseline characteristics between treatment groups.

The demographics and baseline characteristics are presented in Table below for the full analysis set. The patient listing of baseline characteristics for this data set can be found in Appendix 16.2.4.

Table for Demographic and Baseline Characteristics – Full Analysis Set

Variable	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417	p-value[a]
Age (years)				
n	208	209	417	
Mean (SD)	66.8 (5.1)	66.7 (4.8)	66.7 (5.0)	0.957
Minimum-Maximum	60-80	60-80	60-80	
Race				
n	208	209	417	0.446
White	193 (92.8%)	192 (91.9%)	385 (92.3%)	
Black	6 (2.9%)	2 (1.0%)	8 (1.9%)	
Asian	4 (1.9%)	9 (4.3%)	13 (3.1%)	
Hispanic or Latino	2 (1.0%)	1 (0.5%)	3 (0.7%)	
Hawaiian or Other Pacific Islander	1 (0.5%)	2 (1.0%)	3 (0.7%)	
Other	2 (1.0%)	3 (1.4%)	5 (1.2%)	
Weight (kg)				
n	208	209	417	0.907
Mean (SD)	73.5 (14.1)	73.3 (14.5)	73.4 (14.3)	
Minimum-Maximum	46-118	43-126	43-126	
Height (mm)				
n	208	209	417	0.344
Mean	1611.8 (60.7)	1617.3 (59.4)	1614.5 (60.0)	
Minimum-Maximum	1470-1789	1487-1819	1470-1819	
BMI (kg/m^2)				
n	208	209	417	0.597
Mean (SD)	28.3 (5.3)	28.0 (5.3)	28.1 (5.3)	
Minimum-Maximum	18-44	17-47	17-47	
Smoking History				
n	208	209	417	0.552
Smoker n (%)	16 (7.7)	13 (6.2)	29 (7.0)	
Nonsmoker n (%)	192 (92.3)	196 (93.8)	388 (93.0)	
Number of Cigarettes (per day)				
n	16	13	29	0.536
Mean (SD)	10.6 (7.2)	11.4 (9.5)	11.0 (8.2)	
Minimum-Maximum	3-30	1-30	1-30	

(continued)

N = total number of patients; n = number of patients with data available; SD = standard deviation.
a Treatment effect P-values for continuous data are obtained from an ANOVA model, with terms for treatment and center. Treatment effect P-values for categorical data are obtained from the generalized Cochran-Mantel-Haenszel test, stratified by center. Reference: Table 8

Table for Demographic and Baseline Characteristics - Full Analysis Set (continued):

Variable	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417	p-value[a]
Alcohol Intake (in past 30 days)				
n	208	208	416	0.804
Every day n (%)	12 (5.8)	11 (5.3)	23 (5.5)	
5-6 days/week n (%)	15 (7.2)	18 (8.6)	33 (7.9)	
3-4 days/week n (%)	17 (8.2)	17 (8.1)	34 (8.2)	
1-2 days/week n (%)	31 (14.9)	29 (13.9)	60 (14.4)	
2-3- times in past 30 days n (%)	35 (16.8)	40 (19.1)	75 (18.0)	
Once in past 30 days n (%)	24 (11.5)	24 (11.5)	48 (11.5)	
Not at all in past 30 days n (%)	74 (35.6)	69 (33.0)	143 (34.3)	
Alcohol Intake (drinks per day)				
n	134	139	273	0.984
Mean (SD)	0.5 (0.6)	0.5 (0.6)	0.5 (0.6)	
Minimum-Maximum	0-3	0-4	0-4	
Calcium Intake (mg per day)				
n	208	208	416	0.206
Mean (SD)	745.5 (447.3)	691.1 (424.6)	718.3 (436.4)	
Minimum-Maximum	60-3087	104-3999	60-3999	

N = total number of patients; n = number of patients with data available; SD = standard deviation.
a Treatment effect P-values for continuous data are obtained from an ANOVA model, with terms for treatment and center. Treatment effect P-values for categorical data are obtained from the generalized Cochran-Mantel-Haenszel test, stratified by center. Reference: Table 8 (in the NDA)

In the "Completers" set of patients, there were baseline imbalances with respect to Baseline Bone Mineral Density (g/ cm2) of Lumbar Spine (AP View, L2- L4) (and baseline Bone Mineral Density T- score Classification too).

2.3.3.1.4 Measurements of Treatment Compliance and Other Factors That Could Affect Response

The sponsor reported details on "Gynecological history," "Medical and surgical history," "T- scores (lumbar spine and/ or total hip) at baseline," "Concomitant Medications," "Hip and spine surgery and artifacts or hardware in place," and "Treatment Compliance" on pages 57 to 61 of the Study Report (in the NDA).

For the ultra-low estradiol treatment group, approximately 95% and 94% of patients had a rate of compliance that exceeded 75% at 12 and 24 months, respectively. For the placebo patients, approximately 96% and 90% had a rate of compliance that exceeded 75% at 12 and 24 months, respectively.

There was no statistical difference between treatment groups in the distribution of patients by compliance rate category. The following Table represents the compliance rate by treatment group. The compliance questionnaire and a by-patient assessment of compliance can be found in Appendix 16.2.5 (of the NDA).

Compliance Rate by Treatment Group - Full Analysis Set

Time Period/ Compliance Rate	Statistic	Ultra-low Estradiol	Placebo	Total	P-value
Overall 12 month[a] compliance	n, mean % (SD)	194, 98.7% (15.8)	191, 99.7% (16.3)	384, 99.2% (16.1)	0.554
<50%	n (%)	5 (2.6)	7 (3.7)	12 (3.1)	0.227
50% to 75%	n (%)	5 (2.6)	1 (0.5)	6 (1.6)	
>75%	n (%)	184 (94.8)	182 (95.8)	366 (95.3)	
Overall 24 month[b] compliance	n, mean % (SD)	188, 96.3% (18.8)	182, 96.6% (21.1)	369, 96.6% (19.8)	0.808
<50%	n (%)	9 (4.8)	9 (5.0)	18 (4.9)	0.186
50% to 75%	n (%)	3 (1.6)	9 (5.0)	12 (3.3)	
>75%	n (%)	176 (93.6)	163 (90.1)	339 (91.9)	

n = number of patients with data available; SD = standard deviation.
[a]Baseline to 12-month (or final) visit
[b]Baseline to 24-month (or final) visit.
Note: For each interval between visits a percent compliance was determined by dividing the number of patches worn by the length of the reporting period x 100. It will be assumed each patch was worn for 7 days. Compliance > 100% due to replaced patches will be rounded to 100%. A weighted average of these interval-specific compliance percentages was computed, with weights given by the proportion of the total study duration in each reporting period.
No adjustments were made for multiple comparisons. The p-values are the result of a t-test for continuous data and a chi-squared test for categorical data that test for group differences between ultra-low estradiol and placebo groups

The sponsor provided baseline treatment comparison p-values for the characteristics considered so far but not for what follows in this Section.

§ Considering various factors (details on one are presented below) under the **gynecological history**, the placebo group appears to be of more reproductive potential at baseline.

Variable	Statistics	Ultra-low Estradiol	Placebo	Total
	N	208	209	417
Age when 1 Ovary Removed (years)	n	7	5	12
	Mean (SD)	27.3 (11.6)	38.6 (14.5)	32.0 (13.5)
	Minimum-Maximum	16-50	22-54	16-54

N = total number of patients; n = number of patients with data available; SD = standard deviation.
Reference: Table 9

§ Table for **Medical and Surgical History** by Body System and Treatment Group - Safety Set:

Number (%) of Subjects

Body System	E2 ultralow	Placebo
Total No. of Subjects	208	209
H.E.E.N.T.		
Normal	17 (8.2)	29 (13.9)
Abnormal	191 (91.8)	180 (86.1)
Not Done	0 (0)	0 (0)
Respiratory		
Normal	153 (73.6)	147 (70.3)
Abnormal	55 (26.4)	62 (29.7)
Not Done	0 (0)	0 (0)
Cardiovascular		
Normal	95 (45.7)	113 (54.1)
Abnormal	113 (54.3)	96 (45.9)
Not Done	0 (0)	0 (0)
Gastrointestinal		
Normal	107 (51.4)	98 (46.9)
Abnormal	101 (48.6)	111 (53.1)
Not Done	0 (0)	0 (0)

With 2-sided Fisher's exact tests, the two treatments are statistically only marginally non-significant with respect to groups, the 1st and the 3rd categories (H.E.E.N.T. and Cardiovascular).

§ **T- scores** (lumbar spine and/or total hip) at baseline

The majority (214 [51.3%]) of patients randomized had spine and/or hip T-scores of =- 1 to >- 2.5 at baseline, and were considered to be osteopenic. Less than 20% of the total randomized patients were considered to be osteoporotic (had T- scores of =- 2.5) at baseline. Table below describes the distribution of patients by categories of T- scores.

BMD T-score at Baseline	Ultra-low Estradiol N= 208	Placebo N = 209
	n (%)	n (%)
>-1	60 (28.8)	74 (35.4)
≤-1 to >-2.5	107 (51.4)	107 (51.2)
≤-2.5	41 (19.7)	28 (13.4)

(Notes continued)

BMD = bone mineral density; N = total number of patients; n = number of patients with data available.
Reference: Table 11

§ **Concomitant medications** were allowed except for those (e.g., estrogen and/or progestin therapy, systemic fluoride, calcitonin and bisphosphonates) identified in the exclusion criteria. The majority of selected concomitant medications identified at baseline were cortiçosteroids that were indicated for musculoskeletal or other skin or systemic inflammatory complaints. The operations manual used at each site indicated that medications for osteoporosis and hormone replacement therapy were excluded; patients who received these medications during the study were discontinued from study medication. During the study, 12 patients reported medications that were excluded according to the operations manual. All patients except for 1 ultra-low estradiol patient (No. 100091) and 1 placebo patient (No. 001260) had stopped study medication before starting 1 of the excluded medications. The ultra-low estradiol patient received Fosamax for 10 days prior to discontinuation of study medication, and the placebo patient received Estrace for 6 days following Visit 2.

Number and Percentage of Subjects With Concomitant Medication by Treatment Group

	Number (%)		
Medication Name	E2 Ultralow	Placebo	Total
Total Number of Subjects	208	209	417
Number of Subjects with any Concomitant Medication	24(11.5)	23(11.0)	47(11.3)
ACETONIL	0(0.0)	1(0.5)	1(0.2)
ADVAIR	1(0.5)	0(0.0)	1(0.2)
ANUSOL-HC SUPPOSITORIES	0(0.0)	1(0.5)	1(0.2)
AYGESTIN	1(0.5)	0(0.0)	1(0.2)
CELESTONE	0(0.0)	1(0.5)	1(0.2)
CORTISONE INJECT	1(0.5)	0(0.0)	1(0.2)
CORTISONE	0(0.0)	1(0.5)	1(0.2)
CORTISONE CREAM 1%	0(0.0)	1(0.5)	1(0.2)
CORTISONE INJECTION	1(0.5)	3(1.4)	4(1.0)
CORTISONE SHOT	1(0.5)	0(0.0)	1(0.2)
CORTISONE SHOT X3	1(0.5)	0(0.0)	1(0.2)
DEPRO MEDROL	1(0.5)	0(0.0)	1(0.2)
DEXAMETHASONE DEXPAK	0(0.0)	1(0.5)	1(0.2)
ECONOPRED	1(0.5)	0(0.0)	1(0.2)

Subjects with more than one use of same concomitant medication will be counted once. Only selected concomitant medications were recorded in the CRF. A list of these medications is found in Appendix 6 of the protocol.

§ Hip and spine surgery and artifacts or hardware in place

At each visit that a DXA scan was performed patients were questioned regarding surgery, or the surgical placement of any hardware, e.g., screws, rods, or prostheses in the lumbar spine or hips, which may affect the accuracy of DXA scanning. In all cases where hip surgery had been performed, the contralateral hip was scanned for the BMD measurements.

A complete listing of the questions asked can be found in Appendix 16.2.6 (of the NDA) and the answers can be found in Appendix 16.2.6 (of the NDA) for screening visit 2, baseline, and subsequent visits, respectively.

2.3.3.1.5 Efficacy Results (Sponsor's Analyses)

The sponsor stated in the Data Analysis Plan (submitted on 2003-11-14):

> "Continuous variables of interest will be analyzed with a two-way Analysis of Covariance (ANCOVA) with treatment, center, and the treatment by center interaction as factors in the model and baseline as a covariate. If the interaction term is not significant at the 0.05 level of significance, it will be dropped from the model. Otherwise, the treatment-by-center interaction will be retained in the model and summary statistics will be presented by center. In this case, exploratory analysis will be performed to identify reasons for the interaction and outlying centers if any. An outlying center is defined as a center for which the treatment effect is opposite in sign to that for the majority of the centers. If outlying centers are detected, a subset of centers will be analyzed after removing the outlying centers.
>
> If the assumption of homogeneity of the slopes in the ANCOVA model is violated at the 0.05 level of significance, the ANOVA model will be used in place of the ANCOVA model.
>
> The normality of residuals will be assessed for each efficacy variable separately using the Shapiro-Wilk Test3 at the 12 and 24 month endpoints. If the Shapiro-Wilk Test is significant at the 0.05 level of significance, a non-parametric analysis, rank ANCOVA, with terms for treatment, center, and baseline, will be performed. The two-way ANOVA after rank transformation yields a valid test for the treatment difference when the treatment-by-center interaction term is excluded from the model. For non-normal data, there is no satisfactory test for the interaction. The assumption of homogeneity of variances will be made without making any statistical test.
>
> Furthermore, the results of the treatment visits will be compared with baseline values within each treatment group using the paired t-test.
>
> Binary variables of interest will be analyzed with a logistic regression model with terms for treatment, center, and the treatment-by-center interaction in the model. The treatment-by-center interaction term will be excluded from the model if it is not significant at the 0.05 level of significance or the model fails to converge due to sparse data. ... The 24 Month endpoint analysis of percent change from baseline in BMD of lumbar spine (AP view L2-L4) is the primary efficacy

analysis. The analysis methods described above for continuous variables will be used to compare the change and percent change from baseline in BMD lumbar spine and total hip at the 12 Month and 24 Month endpoints as defined in Section 2.12.

In addition, the paired t-test will be used to compare the value of the response variable at each visit to the baseline value within each treatment group. Summary statistics for change from baseline and percent change from baseline will be provided for 12 Month and 24 Month observed data."

§ Results: Primary Efficacy Parameters

Change and Percent Change From Baseline in BMD (g/cm2) for Lumbar Spine - Full Analysis Set

		Visit 3 Month 12	12-Month Endpoint[a]	Visit 6 Month 24	24-Month Endpoint[a]
		Change (%)	Change (%)	Change (%)	Change (%)
Ultra-low Estradiol (N = 208)	n	187	189	173	189
	Mean	0.021 (2.29)	0.021 (2.29)	0.028 (3.05)	0.027 (2.99)
	Median	0.020 (2.19)	0.020 (2.19)	0.031 (3.22)	0.030 (3.18)
	SD	0.029 (3.10)	0.029 (3.10)	0.036 (3.94)	0.036 (3.89)
	Minimum	-0.062 (-6.72)	-0.062 (-6.72)	-0.080 (-6.38)	-0.080 (-6.72)
	Maximum	0.096 (10.30)	0.096 (10.30)	0.142 (20.12)	0.142 (20.12)
Placebo (N = 209)	n	182	186	160	186
	Mean	0.005 (0.58)	0.005 (0.51)	0.007 (0.74)	0.005 (0.54)
	Median	0.003 (0.27)	0.002 (0.16)	0.005 (0.47)	0.005 (0.40)
	SD	0.030 (3.23)	0.030 (3.25)	0.033 (3.60)	0.034 (3.69)
	Minimum	-0.082 (-9.36)	-0.082 (-9.36)	-0.074 (-8.37)	-0.082 (-9.36)
	Maximum	0.094 (11.89)	0.094 (11.89)	0.120 (13.16)	0.120 (13.16)
	p-value[b]		<0.001		<0.001

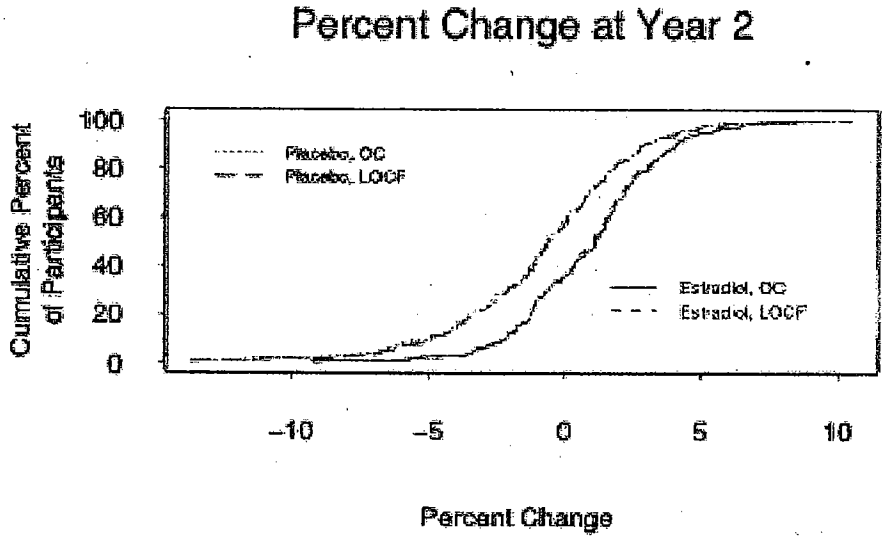
N = total number of patients; n = number of patients with data available; SD = standard deviation.
[a] Represents the last observed postbaseline value (at that time point) carried forward.
[b] P- values are for between-treatment group comparisons of percent change from baseline. Default ANCOVA model has terms for treatment, center, and baseline as a covariate.
Reference: Table 16

Reviewer's Note: From the referenced Table 16, the p-value is <0.001 for both "change" and "percent change" from baseline.

The mean values at baseline were not statistically (p = 0.054) different between the treatment groups, however the ultra-low estradiol patients had a lower mean BMD value (0.936 g/ cm^2) at baseline than did placebo patients (0.955 g/cm^2).

Ultra-low estradiol patients demonstrated a statistically significantly ($p < 0.001$) greater mean percent change from baseline for lumbar spine BMD compared with placebo patients for both the 12- and 24-month endpoints. Mean percent increases for ultra-low estradiol patients were 2.29% and 2.99% at the 12- and 24-month endpoints, respectively, and were 0.51% and 0.54% for placebo patients at the same time points. Therefore, ultra-low estradiol patients experienced a more than 4-fold greater proportional increase (2.29/0.51 = 4.5 and 3.00/0.54 = 5.5) for BMD in their lumbar spine than placebo patients at both the 12-and 24-month endpoints, as demonstrated by percent change from baseline.

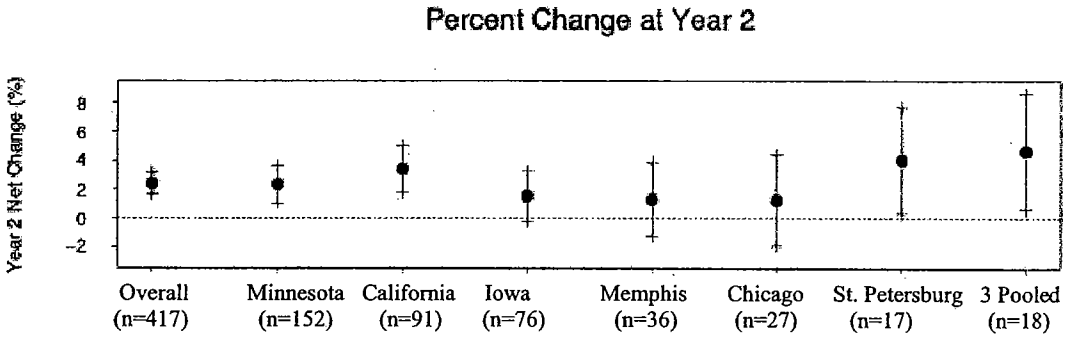
Following is the cumulative distribution graph for Percent Change from Baseline in BMD for Lumbar Spine at Year 2:



From this, percent of patients (y-axis value) with a value of Percent Change from Baseline, smaller than or equal to a value on the x-axis can be read.

§ Even by a worst case analysis using opposite treatment group means for missing observations but using standard error from the non-missing set the results were highly significant (Statistical Appendix 4.5.1 of the NDA).

§ There was no center by treatment interaction. The graph for the 95% confidence intervals for the centers with respect to the difference between two treatments in percent change from baseline follows. The three centers Barbier, S. (500), Pinkerton, J. (600), and Rowe, D. (800) were pooled.



Note: The corresponding Table in the NDA (Statistical Appendix 3.2) has numerical confidence intervals.

2.3.3.1.6 Reviewer's Comments and Conclusions on Study Under Protocol 98188

This study has provided statistical evidence in favor of the efficacy of ultra-low estradiol in the prevention of osteoporosis in postmenopausal women with intact uteri when administered using a transdermal patch placed on the lower abdomen and replaced weekly.

Both this reviewer's analyses and those of Dr. Sahlroot (HFD-715) support this claim.

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot
Dr. Wilson

CC:
Archival NDA 21-674/N_000

HFD-510/Dr. Colman
HFD-510/Dr. Stadel
HFD-700/ Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 5/19/04

This review consists of 22 pages of text.

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

/s/

Japobrata Choudhury
5/20/04 03:36:20 PM
BIOMETRICS

Todd Sahlroot
5/20/04 04:08:21 PM
BIOMETRICS

Steve Wilson
5/21/04 12:00:32 PM
BIOMETRICS