

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-674**

**MEDICAL REVIEW**

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

DATE: June 8, 2004

FROM: David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-674  
Menostar (estradiol transdermal system)  
Berlex Laboratories, Inc.  
Prevention of postmenopausal osteoporosis

SUBJECT: NDA review issues and recommended action

**Background**

Menostar is an “ultra-low-dose” transdermal estradiol product that contains 1.0 mg of 17-beta estradiol and which delivers an approximate daily dose of 0.014 mg daily. This is a type 6 NDA that ultimately will be merged with the NDA for Climara, an identical transdermal estradiol product labeled for use according to all the approved indications for estrogen replacement in postmenopausal and hypogonadal women, and marketed in patches that deliver from 0.025 mg daily up to 0.1 mg daily. Menostar has been studied only for prevention of PMO, will be indicated only for same, and as such, carries a distinct tradename.

This product was developed based on the rationale that very low doses of transdermal estrogen, effective for prevention of osteoporosis, would confer markedly decreased risks of adverse estrogenic effects relative to higher doses of transdermal estrogens and certainly relative to oral estrogens and to estrogen-progestin combinations. Based on a large body of evidence, most recently from the WHI study of both Premarin plus MPA and of Premarin alone, this risk-sparing is expected specifically with regard to breast cancer, cardiovascular risk (MI, stroke), venous thromboembolism, and endometrium. As such, the trial supporting approval of this lowest dose of estrogen that would be available in the U.S. was designed to test the effect of Menostar (unopposed estrogen—not given with a cyclic progestin) vs. placebo on BMD and to evaluate the safety of this dose on the endometrium.

**Clinical Efficacy and Safety**

The product was evaluated in a 2-year, randomized, placebo-controlled study in post-menopausal women aged 60 to 80 years, with Z-scores of the spine or hip greater than -2.0, and no primary or secondary causes for metabolic bone disease. As summarized by Drs. Colman and Stadel, the mean increase in lumbar spine BMD from baseline to month 24 was 3.0% in the Menostar group vs. 0.5% in the placebo group. When the analysis was stratified by baseline serum estradiol levels, patients with E2 level < 5 pg/mL had a mean increase in LS BMD of 3.5% compared to an increase of 0.29% for placebo, while those with E2 ≥ 5 pg/mL had a mean increase in LS BMD of 2.4% compared to a decrease of 1.09% for placebo.

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Drug: Menostar (estradiol transdermal system)

Proposal: prevention of PMO

06/08/04

With regard to uterine effects, at month 12, 5.8% of Menostar patients vs. 1.0% of placebo patients had endometrial proliferation by biopsy. At month 24, these rates were 3.4% and 0%, respectively. Only one woman showed proliferation at both time points. At 24 months, one Menostar patient had atypical endometrial hyperplasia by biopsy. There were no other significant safety imbalances across treatment groups.

The central issue addressed during review was the evidence supporting and the appropriateness of labeling this product for use as unopposed estrogen. The study supporting efficacy in PMO does indeed demonstrate that endometrial stimulation occurs with this product over the two years of use, apparently to a mild degree and evident only in a small minority of patients. Nevertheless, this dose is, apparently, not completely "uterus-neutral." Because of these data, HFD-580 recommended twice yearly progesterone withdrawal with annual endometrial biopsy until further data were available to alleviate fully concerns over risks associated with uterine stimulation. Labeling to this effect has been successfully negotiated with the sponsor.

The other safety issue, not specifically addressed in the application, bears on the extent to which the estrogen and estrogen-progestin "class" labeling adopted by FDA after review of the Prempro arm of the Women's Health Initiative study should be applied to the use of Menostar. Specifically, the class label relegates the use of estrogens and estrogen-progestin drug products for treatment of vulvovaginal atrophy (VVA) and for the prevention of PMO to de facto second-line indications. Specifically, the class label states that if the product is being prescribed solely for the prevention of PMO, it should be considered only for women at high risk of osteoporosis, and non-estrogen therapies should be carefully considered.

As PMO is the sole indication for Menostar, it is illogical to include the phrase "solely for the prevention of PMO," however, it is reasonable at this time to adhere to the class label directing use in high risk women and consideration of other options for prevention of PMO.

Based on a vast body of evidence, including the recently published (but not yet reviewed by FDA) results of the Premarin-alone arm of the WHI study, this low-dose transdermal estrogen must be assumed to be safer than oral estrogens and safer than higher doses of transdermal estrogens. With specific reference to the WHI, in the Premarin alone arm, there was no increased risk of breast cancer, a reduction in hip fracture, no increased risk for MI, and a small increase in risk for venous thromboembolism and for stroke. All this led to a global index of risk equivalent to that with placebo. It was an increased global risk relative to placebo in the Prempro part of the WHI, driven by the increased risk of breast cancer and CV disease, that specifically marked that regimen (Premarin 0.625 mg daily, MPA 2.5 mg daily) as, on average, conferring risks that outweighed benefits).

That said, even though Menostar is a very low dose estrogen product and the method of use calls for progestin only 2 to 4 weeks out of the year in women with a uterus, for now, the class labeling stands, though changes may be forthcoming pending review of the Premarin arm of the WHI.

#### **Labeling**

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As above, final labeling has been negotiated.

**Biopharmaceutics**

No issues.

**Pharmacology/Toxicology**

No specific preclinical studies were conducted as this is simply a lower dose of an approved transdermal system.

**Chemistry/ Microbiology**

Recommendation to approve

**DSI/Data Integrity**

The trial was audited (2 investigators). No forms 483 were issued. No concerns over data integrity.

**Financial disclosure**

The financial disclosure information is in order. No concerns over influences on outcomes.

**ODS/DMETS**

DMETS recommended against the name Menostar, citing possible double dosing with Climara. This is not a concern. There is a clear rationale for separate tradenames, and the risk of double dosing, should it occur, is medically negligible.

**Recommendation**

Approve.

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David Orloff  
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MEDICAL OFFICER

## TEAM LEADER REVIEW

**NDA:** 21-674

**DRUG:** Menostar (transdermal estradiol)

**INDICATION:** Prevention of postmenopausal osteoporosis in women with and without an uterus

**COMPANY:** Berlex

**PRIMARY MEDICAL REVIEWER:** Bruce V. Stadel, MD, MPH

**UFGD<sub>10</sub>:** June 8, 2004

**DATE OF REVIEW:** May 10, 2004

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### Primary Medical Reviewer's Regulatory Recommendation

Dr. Stadel recommends that this NDA be approved.

### Background

Menostar is identical in composition to Climara, a transdermal estradiol product approved for the treatment of vasomotor symptoms, vulvovaginal atrophy, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and the prevention of postmenopausal osteoporosis (PMO). The approved doses are: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.06 mg/day, 0.075 mg/day, and 0.1 mg/day<sup>1</sup>.

Menostar is a 3.25 cm<sup>2</sup> patch containing 1.0 mg of 17-beta estradiol, in which approximately 0.014 mg of active drug is delivered per day; the patch is changed weekly.

If approved, Menostar will be the lowest dose of estrogen approved for prevention of PMO.

### Clinical Study

**Title:** 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.

**Primary Objectives:** The primary efficacy objective of this phase 3 study was to demonstrate the superiority of a low dose of unopposed estradiol, administered transdermally, compared with placebo, in the prevention of osteoporosis of the lumbar spine in postmenopausal women with intact uteri. The primary safety objective of this phase 3 study was to demonstrate the endometrial safety of an unopposed low dose estradiol, administered transdermally, compared with placebo.

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<sup>1</sup> On-line Physician's Desk Reference

## Secondary Objectives:

- To demonstrate the superiority of an unopposed ultra-low dose estradiol, administered transdermally, compared with placebo on bone density of the total hip.
- To demonstrate the effects of unopposed estradiol, administered transdermally, on variables of bone metabolism (serum osteocalcin, carboxyterminal telopeptide of type I collagen (ICTP), serum bone-specific alkaline phosphatase, and urinary deoxypyridinoline/creatinine ratio).
- To evaluate the effect of an unopposed ultra-low dose estradiol, administered transdermally, compared with placebo on 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), Center for Epidemiological Studies Depression Scale, short version (CES-D10), urinary incontinence and sexual function questionnaires.
- To evaluate the effect of an unopposed ultra-low dose estradiol, administered transdermally, compared with placebo on cognitive function.

**Study Design:** This was a multicenter, double-blind, randomized, parallel-group, placebo-controlled 24-month study in postmenopausal women with intact uteri. The study was performed at 9 clinical investigative centers. Study subjects were randomized (1:1) to either a weekly placebo or Menostar patch. All eligible patients first entered a qualification period to assess their tolerance of the transdermal system. All eligible patients were given a placebo 3.25 cm<sup>2</sup> patch and instructed to apply the patch for 1 week to a site on the lower abdomen. Patients who were noncompliant or experienced skin irritation greater than Grade 2 at the patch application site were not enrolled in the study. All participants received 562 mg of elemental calcium and 400 IU of vitamin D per day as supplements.

Patients continued in the clinical trial, participated in all clinic visits and measurements, and were followed for outcomes regardless of whether they took the study medication. Patients were discontinued from the study medication for any of the following reasons: diagnosis of endometrial hyperplasia, endometrial cancer or breast cancer; deep vein thrombosis; pulmonary embolism; active gallbladder disease; prolonged immobilization (for instance, following accidents, fracture, stroke, or surgery); onset of jaundice or clinical hepatitis. Patients whose lumbar spine BMD T score was equal to or less than -3.5 or decreased by an annualized rate of 6% at the 12-month clinic visit could continue to take the study medication; however, they were informed about their rate of bone loss and referred to their primary care physician.

**Patient Population:** Women aged  $\geq 60$  and  $\leq 80$  years who were more than 5 years postmenopausal were eligible for this study. Patients with BMD Z-scores of the spine or hip that were below  $-2.0$  were not eligible for the study. Additional exclusion criteria included:

- Known or suspected bone disease (including osteoporosis); BMD below  $-2Z$  of the lumbar spine (AP view, L2-L4) or total hip; history of hypo- or hyperparathyroidism, Paget's Disease, osteomalacia, osteogenesis imperfecta, or other metabolic disease of bone, hypo- or hypercalcemia; vitamin D deficiencies
- Fracture within 6 months prior to the start of the study
- Pre-existing heart disease (history of myocardial infarction, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, coronary stenting, or angiographic evidence of 50% narrowing of 1 or more coronary arteries)

- History of venous thromboembolic event requiring anticoagulation or current treatment with anticoagulants
- Baseline endometrial biopsy showing simple hyperplasia or worse
- History of stroke or transient ischemic attacks
- Fasting baseline triglycerides  $\geq 300$  mg/dL or glucose  $\geq 180$  mg/dL
- Uncontrolled hypertension; sitting systolic blood pressure  $\geq 180$  mm Hg or sitting diastolic blood pressure  $\geq 105$  mm Hg at rest
- Any history of breast or endometrial cancer, or malignant melanoma; known or suspected malignant or premalignant disease (excluding basal or squamous cancer of the skin) within the past 10 years
- Uncontrolled thyroid disorders, or initiation or change in dose of thyroid replacement therapy within 6 months
- Estrogen or progestin therapy (oral, transdermal, intramuscular, intrauterine or intravaginal administration) within 3 months prior to start of study
- Systemic or gynecologic disorder, laboratory finding, or ultrasonography finding which, in the opinion of the investigator, could have interfered with the conduct of the study or the interpretation of the results
- Current significant liver dysfunction or disease
- Systemic treatment with fluoride, calcitonin, or bisphosphonates at any time
- Participation in another clinical trial involving administration of an investigational drug within the last 1 month prior to study entry

**Endpoints:** The primary efficacy endpoint was a comparison between groups of the change from baseline to Month 24 in lumbar spine BMD, as assessed by DXA. Measurement of BMD of the lumbar spine was also done at Month 12; changes in BMD of the hip were assessed at Months 12 and 24. Serum osteocalcin, bone-specific alkaline phosphatase, ICTP, and urinary deoxypyridinoline crosslinks were assessed at Months 12 and 24 in order to evaluate bone turnover.

The incidence of endometrial hyperplasia was the primary safety variable. In order to monitor for pathologic changes involving the endometrium, patients had endometrial biopsies performed at Visits Month 12, Month 24, and any time when medically indicated. At screening and at Month 12, Month 24, endometrial aspiration biopsies and if needed, transvaginal ultrasonography was performed by the principal investigator and/or associate using procedures consistent with the current clinical practices at each site. At screening, if it was not possible to enter the uterine cavity for endometrial biopsy, the participant was not enrolled. The endometrial sample was sufficient if it contained strips of endometrial epithelium. If tissue obtained at endometrial biopsy was insufficient for diagnosis, vaginal ultrasound was performed and endometrial thickness of less than 4 mm was considered to represent atrophic/inactive endometrium and the patient was eligible to enter the study. Women with an endometrial thickness of  $> 4$  mm at baseline were excluded unless a repeat endometrial biopsy was histologically normal. A central reading laboratory was used for processing and evaluation of the endometrial biopsy slides. All endometrial biopsies were evaluated by 2 independent pathologists, located at different pathology laboratories, blinded to treatment assignment and to each other's reading. If there were discrepancies between the first and second read, a third independent, referee pathologist evaluated the samples in order to settle the dispute and to provide a final diagnosis. This procedure was followed for disputes involving both normal and abnormal diagnoses.

The evaluations determined eligibility for the study, discontinuation from the study and follow-up of study patients. In any patient who developed an abnormal endometrial polyp alone (no adjacent endometrial tissue analyzable) or hyperplasia or any condition more severe at any time during the study, study medication was immediately discontinued and the patient was given appropriate treatment and follow-up. The patient was followed until resolution of endometrial pathology or until a stable clinical state was reached. Also, in cases of prolonged moderate to severe vaginal bleeding (longer than 7 days), transvaginal ultrasonography and/or endometrial biopsy were performed as indicated.

**Statistical Analyses:** Two analysis sets were considered in the course of the efficacy evaluation: the Full Analysis set and the per protocol set. The full analysis set included all patients who were randomized to study medication and had at least 1 post baseline measurement. A patient was included in the Per Protocol set if she was included in the full analysis set, did not take any prohibited medication, had 75% or higher study drug compliance, and had no major protocol violations.

Analysis of the change and percent change in BMD of the spine and hip was done for the members of the full analysis set who were in the following subgroups:

- Patients with osteopenia (T-scores in the interval (-2.5, -1]) at baseline
- Patients with osteoporosis (T-scores  $\leq$  -2.5) at baseline
- Patients with the onset of menopause from 5 to 10 years
- Patients with the onset of menopause greater than 10 years.

## RESULTS

### Efficacy

**Patient Disposition:** A total of 717 patients were screened; 300 of these subjects were not randomized. This left 417 patients who were randomized to either placebo or Menostar once-weekly patches (209 to placebo and 208 to Menostar). Twenty-three percent and 17% of placebo and Menostar subjects discontinued treatment prematurely, respectively. Three percent of placebo and 4% of Menostar subjects discontinued due to an adverse event.

**Patient Demographics:** The two groups were well-matched for baseline characteristics. The mean age was 67 years, 92% were Caucasian, and the average BMI was 28 kg/m<sup>2</sup>. The baseline BMD values were lower in the Menostar group (0.936 g/cm<sup>2</sup>) than in the placebo group (0.955 g/cm<sup>2</sup>) (p=0.054). Fifty-two percent of the women had baseline lumbar spine and/or hip BMD T-scores between -1 and -2.5 (osteopenic); 32% had baseline T-scores of greater than -1; and 17% had T-scores below -2.5.

**Primary Efficacy Outcomes:** In the Full Analysis Set, the adjusted mean increase in lumbar spine BMD from baseline to Month 24 was 3.0% in the Menostar group vs. 0.5% in the placebo group (p<0.001). At Month 12 the changes were 2.3% and 0.5% in the Menostar and placebo groups, respectively (p<0.001).

In the Full Analysis Set, the adjusted mean changes in total hip BMD from baseline to Month 24 were 0.8% and -0.7% (p<0.001). At Month 12 the changes were 0.9% and 0.2% in the Menostar and placebo groups, respectively (p<0.001).

In ancillary analyses, the placebo-subtracted increases in lumbar spine and total hip BMD were of a similar magnitude in the Menostar-treated women who had osteopenic or osteoporotic lumbar spine BMD values at baseline.

In supplementary analyses that Dr. Stadel requested, efficacy was greater in the women who had baseline estradiol levels below 5 pg/ml when compared with those with baseline estradiol levels above 5 pg/ml.

**Secondary Efficacy Outcomes:** Although all the comparisons are statistically significant, the average differences between the Menostar and placebo-treated groups in the changes in markers of bone formation and resorption were of small magnitude.

Quality of life and cognitive function were assessed using a variety of questionnaires. In no case were there statistically or clinically significant differences between the Menostar and placebo-treated groups.

## **Safety**

**Endometrium:** All but one patient in the Menostar group had endometrial biopsies at baseline. Approximately 77% of the women in each group had normal endometrial biopsy results. At Month 12, 5.8% of the Menostar patients and 1.0% of the placebo subjects had proliferative endometrium on biopsy. At Month 24, 3.4% of Menostar and 0% of the placebo women had proliferative endometrium on biopsy and one Menostar subject had atypical endometrial hyperplasia. These findings did not differ significantly when evaluated by baseline level of estradiol (< 5 pg/ml vs. ≥ 5 pg/ml).

**Deaths:** There were no deaths in the trial.

**Serious AEs:** The incidences of serious AEs were 11.0% in placebo and 11.5% in the Menostar group. Overall, the number of patients in either treatment group with a serious AE was very low and there were no meaningful imbalances between groups for any single serious AE. The incidence of serious AEs in the Cardiovascular System was 3.3% in the placebo group and 1.4% in the Menostar group. In Table 44 of the sponsor's submission, there is one report of breast cancer in the Menostar group and 2 in the placebo group.

**Breast Cancer:** One Menostar and 2 placebo subjects were diagnosed with breast cancer during the study.

**Adverse Events Leading to Withdrawal:** Ten percent of the patients in each group discontinued prematurely due to an adverse event. Flatulence was the most common AE leading to withdrawal in the Menostar group.

**Treatment-Emergent AEs:** The only treatment-emergent AE with a reported incidence that was significantly higher in the Menostar vs. the placebo group was leukorrhea (10% vs. 1.4%). According to Dr. Stadel's review, there were 13 patients in the Menostar group and 4 women in the placebo group who were coded as having cervical neoplasm. All but one of these cases (in the placebo group) represented endocervical polyps. All but one of the women had an endometrial biopsy at Month 12 and/or 24. I patient in the Menostar group had "atypical stroma/adenocarcinoma"; all others had benign findings or "tissue insufficient for diagnosis".

**Fractures:** Fractures were reported as adverse events only; there was no systematic attempt to record the incidence of fractures. Four Menostar patients had a total of 6 fractures; whereas, 10 of the placebo patients had a total of 13 fractures. Most of these were reportedly traumatic fractures.

**Lipids:** The mean levels of total cholesterol and LDL cholesterol decreased from baseline to Month 24 in both groups; the difference between groups was not significant, clinically or statistically. The mean levels of TG increased from baseline to Month 24 by a small amount in both groups such that the difference between groups was not significant. Levels of HDL did not change from baseline to Month 24 in either group.

**Misc:** There were no clinically meaningful changes in blood chemistries, blood pressure, pulse, or body weight in either treatment group.

**HFD-580 Consult on Endometrial Findings:** Dr. Phill Price, a medical officer from HFD-580, has provided the Division with a review of the endometrial safety data from the Menostar clinical trial. The upshot of Dr. Price's recommendation is that all women with a uterus should receive 14 days of a progestin every 6 months while taking Menostar. If the sponsor generates long-term data which indicate that unopposed Menostar does not stimulate the endometrium, the labeling for the drug could be amended to allow use of Menostar without a progestin.

HFD-580 also commented that if the sponsor does not accept the above proposal, the labeling should include a recommendation that all patients should have endometrial biopsies at yearly intervals. If any proliferation is demonstrated, patients should then receive a progestin.

**DSI Inspection:** In a memorandum dated 29 April 2004, Ms. Andrea Slavin reported that her inspection of two clinical sites revealed no major violations. She concluded that the data generated from these two sites were acceptable. In a separate inspection of a clinical site run by Dr. Kristine Endsrud, DSI disclosed several violations. All of the violations involved evaluating study subjects over the phone rather than in-person, as required by the protocol. These patients did not have their vital signs evaluated. These violations would not be expected to affect the safety findings from the study.

**Financial Disclosure:** The sponsor has provided the appropriate financial disclosure information. Of note, one investigator, Dr. Bruce Ettinger, as co-inventor of the "ultra low-dose estrogen treatment for postmenopausal osteoporosis" has proprietary interests in the product that was tested. Dr. Ettinger was one of the clinical sites that was inspected by DSI and no irregularities were noted.

**Trade Name – DMETS Consult:** In their consult dated 1 April 2004, DMETS recommended that the trade name Menostar not be approved. DDMAC however, did not find Menostar to be too promotional and accepted the proposed name. Because Menostar is the lowest dose of estrogen in the Climara line of products, DMETS is concerned that some women could be inadvertently receive both products at the same time.

I don't find DMETS concern regarding the trade name Menostar convincing. The dose of Menostar, 0.014 mg per day, is extremely low and even in the event that this product were used with another estrogen product, the incremental increase in estrogen exposure due to the Menostar would, for most women, not be of clinical significance.

#### **Comments**

When approved, Menostar will be the lowest available dose of estrogen indicated for the prevention of PMO. The sponsor has provided adequate evidence that Menostar produces clinically and statistically significant increases in lumbar spine and hip BMD relative to placebo over a 2 year period. Exploratory analyses conducted at the request of Dr. Stadel, suggest that women with baseline levels of estradiol < 5 pg/ml have greater increases in BMD when compared with women with baseline levels  $\geq$  5 pg/ml. These data are biologically plausible, are of value to the clinician, and will be included in the labeling.

Two labeling issues merit discussion.

The first is related to the use of a concomitant progestin to reduce the risk for atypical endometrial hyperplasia and ultimately cancer. Berlex originally proposed that patients with a uterus did not need to take a progestin concomitantly with Menostar because the dose of estrogen was so low that it would not stimulate the endometrium to the point where hyperplasia and cancer would develop.

The fact that one woman treated with Menostar developed atypical hyperplasia of the endometrium during the second year of treatment argues against Berlex's claim that Menostar has a neutral effect on uterine epithelial cells.

Consultants from HFD-580 recommend that all women with a uterus receive 14 days of a progestin every 6 months and a yearly endometrial biopsy to enhance the safe use of Menostar. These recommendations are not based on controlled data that directly address this issue; rather, they represent the collective wisdom of the clinical reviewers from the Division of Reproductive and Urological Drugs. We have had extensive discussion of the concomitant progestin issue with members of HFD-580 and with Berlex.

The latest proposal from Berlex is to include the following language in the Dosage and Administration section of the labeling:

*It is recommended that women who have a uterus and are treated with Menostar<sup>TM</sup> receive a progestin for 14 days every 6 to 12 months and undergo an endometrial biopsy at yearly intervals or as clinically indicated*

The company has submitted rationale in support of their proposed language, as provided below.

- a. No risk of endometrial hyperplasia was observed with Menostar at 1 year in the ULTRA study and the risk at 2 years appears to be low and comparable to currently available combination hormone therapy products and the background incidence in patients without treatment.
- b. A low risk of endometrial hyperplasia with Menostar at 6 months suggested by the clear dose-response relationship of estrogen and endometrial hyperplasia.
- c. A recent Cochrane Collaboration meta-analysis that showed no increased risk of hyperplasia with unopposed low dose estrogen at 6, 12 and 24 months. Even the lowest doses of estrogen studied in this analysis were higher than the estrogen dose delivered by Menostar. In contrast, moderate and high doses of unopposed estrogen were associated with higher rates of endometrial hyperplasia at 6, 12 and 24 months.
- d. Assuming that women who bleed when given a progestin will undergo a work-up, and that 11.7% of women receiving this progestin-based evaluation will have false-positive results. The expense, inconvenience, potential treatment-related risks, and disruption of the traditional schedule of annual visits could only be justified in the presence of a demonstrable and meaningful risk difference between biannual and annual screening.

I find the rationale from C, a meta-analysis from the Cochrane Collaboration<sup>2</sup>, the most persuasive. In a sample of about 600 patients treated with low-dose estrogen: 1-10 mcg of ethinyl estradiol or 0.3 mg esterified estrogens, or placebo, the odds ratio for endometrial hyperplasia was 1.6 (0.22, 11.0) at 6 months; 2.7 (0.70, 10.4) at 12 months; and 1.7 (0.6, 4.7). None of these estimates are of nominal statistical significance.

These low-dose estrogen data contrast with those from patients treated with 0.625 mg of conjugated equine estrogens, a moderate dose. In a sample of approximately 120 patients (half treated with estrogen and half with placebo), the odds ratio for endometrial hyperplasia was 5.4 (1.4, 21.0) at 6 months. In a sample of about 375 patients (half on drug and half on placebo), the odds ratio for endometrial hyperplasia was 8.3 (4.2, 16.2) at 12 months. In a sample of 450 patients (roughly half treated with

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<sup>2</sup> Lethaby, A. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *The Cochrane Library* 2003, Issue 1

placebo and the other half treated with a variety of doses of estrogen, ranging from 0.625 mg to 2.0 mg), the odds ratio for endometrial hyperplasia was 9.6 (6.0, 15.5).

Although the data are limited in scope and within-study comparisons of low and moderate doses of estrogen are not available, the information provided in this meta-analysis does support the idea that the risk of endometrial hyperplasia from unopposed estrogen is directly related to dose and duration of use.

Given these data and the other supporting material provided by the sponsor, I believe it is reasonable to allow the proposed language for the Dosing and Administration section of the labeling to read:

*It is recommended that women who have a uterus and are treated with Menostar<sup>TM</sup> receive a progestin for 14 days every 6 to 12 months and undergo an endometrial biopsy at yearly intervals or as clinically indicated*

The second labeling issue relates to the Indications and Usage section. Berlex originally proposed that this section read: *Menostar is indicated for the prevention of postmenopausal osteoporosis.*

The Indications and Usage section of the current class labeling for estrogen + progestin and estrogen alone products, which is based primarily on the findings of the Prempro arm of the WHI study, reads as follows for the PMO indication: ..... "*When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be only considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.*

Although Dr. Stadel initially supported Berlex's proposed language, which did not contain the wording from the class labeling, after extensive internal discussion with members of HFD-580, all now agree that the most appropriate action would be to make the Menostar Indications and Usage section conform to the class labeling. For obvious reasons, the part that reads, "*When prescribing solely for the prevention of postmenopausal osteoporosis,.....*" should not be included in the Menostar labeling.

**Regulatory Recommendation**

Approve

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## CLINICAL REVIEW

### MEDICAL SAFETY REVIEW

#### Division of Metabolic and Endocrine Drug Products (HFD-510)

**Application #:** 21-674

**Application Type:** New Drug Application

**Sponsor:** Berlex Laboratories, Inc.

**Proprietary Name:** Menostar™

**USAN Name:** Estradiol

**Pharmaceutical**

**Route of**

**Category:** Estrogen

**Administration:** Transdermal

**Indication:** Postmenopausal  
Osteoporosis

**Dosage:** 0.014 mg per day

**Reviewer:** Bruce V. Stadel, MD, MPH

**Dates of Review:** 8 August 2003 to 9 May 2004

**Other Reviewers:** **Chemistry:** Amit Mitra, PhD; **Biopharmaceutics:** Johnny Lau, PhD;

**Pharmacology & Toxicology:** Karen Davis-Bruno, PhD; **Statistics:** Japo Choudhury PhD & Todd Sahlroot PhD

**REVIEW SUMMARY:** Menostar™ was studied in a 2-year randomized clinical trial with lumbar spine bone mineral density (BMD) as the primary efficacy outcome. In women with baseline estradiol (E2) <5pg/ml, Menostar™ increased lumbar spine BMD by a mean of 3.50% compared to a mean increase of 0.29% for placebo (p<0.001), and increased total hip BMD by a mean of 1.04% compared to a mean decrease of 1.09% for placebo (p<0.001), at the 24-month endpoint. In women with baseline E2 ≥5 pg/ml, Menostar™ increased lumbar spine BMD by a mean of 2.40% compared to a mean increase of 0.81% for placebo (p<0.001), and increased total hip BMD by a mean of 0.61% compared to a mean decrease of 0.31% for placebo (p=0.045), at the 24-month endpoint. The only meaningful safety results were an increase in endometrial proliferation and 1 case of hyperplasia. The percentages of women with endometrial proliferation were 5.8% in the Menostar™ group compared to 1.0% in the placebo group at the 12-month endpoint, and 3.4% in the Menostar™ group compared to none in the placebo group at the 24-month endpoint; only 1 woman had proliferation at both endpoints. There was no apparent relationship between baseline E2 and endometrial proliferation. In the Menostar™ group at the 24-month endpoint, 1 woman had atypical endometrial hyperplasia; also, 1 woman had an endocervical polyp with adenocarcinoma, a malignancy not associated with estrogen therapy. "It is recommended that class labeling for estrogen and estrogen/progestin products be adopted for Menostar™. If the sponsor elects not to use estrogen class labeling, all bleeding should be investigated by biopsy and all patients should be biopsied at yearly intervals until long term safety data is obtained showing no proliferative effect on the endometrium." "If any proliferation is demonstrated with biopsy, that patient should be treated with a progestin."

**OUTSTANDING ISSUES:** None

**RECOMMENDED REGULATORY ACTION:**

N drive location:

New clinical studies

Clinical Hold

Study May Proceed

NDA, Efficacy/Label supplement:

Approvable

Not Approvable

Approve

**SIGNATURES:**

**Medical Reviewer:** Bruce V. Stadel, MD, MPH

**Date:** 13 May 2004

**Medical Team Leader:** \_\_\_\_\_

**Date:** \_\_\_\_\_

## CLINICAL REVIEW

**NDA 21-674**  
**Menostar™ (estradiol transdermal system)**  
**Berlex Laboratories**

**Bruce V. Stadel, MD, MPH**  
**Medical Officer**  
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**Documents Reviewed:** This review was based on: the electronic NDA; the chemistry review by Dr. Amit Mitra, biopharmaceutics review by Dr. Johnny Lau, pharmacology/toxicology review by Dr. Karen Davis-Bruno, statistical review by Drs. Japo Choudhury and Todd Sahlroot; consultations with Dr. Phill Price, Division of Reproductive & Urologic Drug Products, Dr. Laura Pincock, Division of Drug Marketing, Advertising, & Communications, and Ms. Jeanine Best, Division of Surveillance, Research, & Communication Support, Ms. Andrea Slavin, Division of Scientific Investigations; and published literature.

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On Original

# CLINICAL REVIEW

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## Executive Summary Section

### Clinical Review for NDA 21-674

#### Executive Summary

#### 1. Recommendations

##### 1.1 Approvability

Approve.

Request that Berlex revise labeling to: (1) show efficacy in the RCT separately for women with baseline E2 <5 pg/mL and  $\geq$ 5 pg/mL; (2) either provide class labeling for estrogen and estrogen/progestin drug products, or state that all bleeding should be investigated by endometrial biopsy, that all patients should be biopsied at yearly intervals until long-term results show no proliferative effect on the endometrium, and that, if any is proliferation found at biopsy, the patient should be treated with a progestin; (3) be consistent with the labeling for Climara, except where there are specific differences for Menostar.

##### 1.2 Phase 4 Studies and/or Risk Management Steps

Optional phase 3 study to further evaluate benefits and risks according to levels of endogenous estrogen before treatment, and for women in races/ethnic groups other than Caucasian. This could include studying ways to minimize the need to use progestin for endometrial safety.

#### 2. Clinical Findings

##### 2.1 Overview of Clinical Program

There were 2 clinical trials: (1) The Clinical Pharmacology study, a Phase 1, 7-day, randomized, crossover, open-label, single center clinical trial. The patients were 18 Caucasian postmenopausal women 60-80 years of age. The study compared Menostar™ (transdermal 17- $\beta$ -estradiol, 0.014 mg per day) to the Climara reference patch; (2) the RCT, a Phase 3, 24-month, randomized, placebo-controlled parallel-group, double-blind, multi-center, clinical trial. The patients were 417 postmenopausal women 60-80 years of age, 92.3% Caucasian, 3.1% Asian, 1.9% Black, 0.7% Hawaiian/other Pacific Islander, and 1.2% other. The RCT compared Menostar™ to placebo. The primary efficacy outcome was change from baseline in lumbar spine BMD. The primary safety outcome was endometrial proliferation and hyperplasia.

## CLINICAL REVIEW

### Executive Summary Section

#### 2.2 Efficacy

Menostar™ is effective for increasing BMD in postmenopausal Caucasian women. It is probably also effective in postmenopausal women of other racial/ethnic groups, although this has not been shown in a randomized clinical trial. Menostar™ is more effective in women with lower compared to higher levels of endogenous estrogen before treatment.

The main efficacy analyses from Berlex showed that:

Lumbar Spine. At baseline, mean lumbar spine BMD was 0.936 g/cm<sup>2</sup> in the Menostar™ group and 0.955 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar™ increased lumbar spine BMD by a mean of 2.29% compared to an mean increase of 0.51% for placebo, p<0.001. At the 24-month endpoint, Menostar™ increased lumbar spine BMD by a mean of 2.99% compared to a mean increase of 0.54% for placebo, p<0.001.

Total Hip. At baseline, mean total hip BMD was 0.835 g/cm<sup>2</sup> in the Menostar™ group and 0.840 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar™ increased total hip BMD by a mean of 0.90% compared to a decrease of 0.22% for placebo, p<0.001. At the 24-month endpoint, Menostar™ increased total hip BMD by a mean of 0.84% compared to a mean decrease of 0.71% for placebo, p<0.001.

At both endpoints, larger percentages of patients in the Menostar™ group compared to the placebo group had no loss in lumbar spine BMD and no loss in total hip BMD, p<0.001 for each comparison.

The main efficacy analyses I requested showed that:

Lumbar Spine, baseline E2 <5 pg/mL. At baseline, mean lumbar spine BMD was 0.920 g/cm<sup>2</sup> in the Menostar™ group and 0.938 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar™ increased lumbar spine BMD by a mean of 2.52% compared to an mean increase of 0.47% for placebo, p<0.001. At the 24-month endpoint, Menostar™ increased lumbar spine BMD by a mean of 3.50% compared to a mean increase of 0.29% for placebo, p<0.001.

Lumbar Spine, baseline E2 >5 pg/mL. At baseline, mean lumbar spine BMD was 0.954 g/cm<sup>2</sup> in the Menostar™ group and 0.975 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar™ increased lumbar spine BMD by a mean of 2.04% compared to an mean increase of 0.55% for placebo, p<0.001. At the 24-month endpoint, Menostar™ increased lumbar spine BMD by a mean of 2.40% compared to a mean increase of 0.81% for placebo, p<0.001.

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Total Hip, Baseline E2 <5 pg/mL. At baseline, mean total hip BMD was 0.822 g/cm<sup>2</sup> in the Menostar™ group and 0.828 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar™ increased total hip BMD by a mean of 1.03% compared to a decrease of 0.64% for placebo, p<0.001. At the 24-month endpoint, Menostar™ increased total hip BMD by a mean of 1.04% compared to a mean decrease of 1.09% for placebo, p<0.001.

Total Hip, Baseline E2 >5 pg/mL. At baseline, mean total hip BMD was 0.850 g/cm<sup>2</sup> in the Menostar™ group and 0.854 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar™ increased total hip BMD by a mean of 0.76% compared to a decrease of 0.24% for placebo, p=0.163. At the 24-month endpoint, Menostar™ increased total hip BMD by a mean of 0.61% compared to a mean decrease of 0.31% for placebo, p=0.045.

### 2.3 Safety

Menostar causes endometrial proliferation in some women, which could increase the risk of hyperplasia or carcinoma. In the Berlex analyses and mine, the only meaningful safety results were an increase in endometrial proliferation and 1 case of hyperplasia. The percentages of women with endometrial proliferation were 5.8% in the Menostar group compared to 1.0% in the placebo group at the 12-month endpoint, and 3.4% in the Menostar group compared to none in the placebo group at the 24-month endpoint; only 1 woman had proliferation at both endpoints. There was no apparent relationship between baseline E2 and endometrial proliferation. In the Menostar group at the 24-month endpoint, 1 woman had atypical endometrial hyperplasia; also, 1 woman had an endocervical polyp with adenocarcinoma, a malignancy not associated with estrogen therapy. *"It is recommended that class labeling for estrogen and estrogen/progestin products be adopted for Menostar. If the sponsor elects not to use estrogen class labeling, all bleeding should be investigated by biopsy and all patients should be biopsied at yearly intervals until long term safety data is obtained showing no proliferative effect on the endometrium."* *"If any proliferation is demonstrated with biopsy, that patient should be treated with a progestin."* See consult on endometrial effects by Dr. Phill Price.

### 2.4 Dosing

Weekly application of transdermal system, as proposed by Berlex Laboratories, Inc.

### 2.5 Special Populations

Little information is available for races/ethnic groups other than Caucasian.

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## Clinical Review Section

### Clinical Review

#### 1. Introduction and Background

##### **Abbreviations used in the text (alphabetical order)**

AE = adverse event, SAE = serious adverse event  
AP = anteroposterior  
Berlex = Berlex Laboratories, Inc.  
BP = blood pressure  
BMD = bone mineral density  
Climara = Climara®  
Climara reference patch = Climara 6.5 cm<sup>2</sup> patch  
CFR = Code of Federal Regulations  
CPMP – Committee for Proprietary Medicinal Products  
Cave = concentration/average  
Cmax = concentration/maximum  
CI = confidence interval  
CYP450, CYP3A, and CYP4A = cytochrome P450 enzymes  
DXA = dual-energy x-ray absorptiometry  
E2 = estradiol = 17-β estradiol  
FSH = follicle stimulating hormone  
Hg = mercury  
IU = International Units, mIU = milli-International Units  
J Clin Endocrinol Metab = Journal of Clinical Endocrinology and Metabolism  
LOCF = last observation carried forward  
L = liter, dL = deciliter, mL = milliliter  
L2-L4 = lumbar vertebrae 2-4  
g = gram, kg = kilogram, mcg = microgram  
Menostar = Menostar™  
m = meter, cm = centimeter, mm = millimeter  
N Engl J Med = New England Journal of Medicine  
Obstet Gynecol – Obstetrics and Gynecology  
%CV = percent coefficient of variation  
pg/mL = picograms/milliliter  
RCT = Randomized, placebo-controlled, parallel-group, double-blind,  
clinical trial  
SHBG = sex hormone binding globulin

#### 1.1 **Established and Proposed Trade Names, Drug Class, Proposed Indication, Dose and Regimen**

Established name: 17-β estradiol.

Proposed trade name: Menostar.

Drug class: estrogen.

Proposed indication: prevention of postmenopausal osteoporosis.

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Proposed dose and regimen: 0.014 mg per day of 17- $\beta$  estradiol, delivered by a 3.25 cm<sup>2</sup> patch containing 1.0 mg 17- $\beta$  estradiol, changed weekly. Menostar is identical in composition to Climara, which is approved and marketed for the relief of vasomotor symptoms and the prevention of postmenopausal osteoporosis. Menostar is cut from the same rollstock as Climara, to 1/2 the size of the lowest-dose Climara patch.

#### 1.2 Treatments Available for the Indication

The most important measures for the prevention of postmenopausal osteoporosis are adequate intakes of calcium and vitamin D, and weight-bearing exercise. The approved drug products are brands of estrogen and estrogen/progestin, and two bisphosphonates, alendronate and risedronate.

#### 1.3 Product Development

See Regulatory History (Appendix 1). See also Climara Prescribing Information (Appendix 2), because Menostar is qualitatively identical to Climara, and 1/2 the size of the Climara reference patch.

#### 1.4 Important Issues with Related Drugs

The benefits and risks of estrogens depend on the specific estrogen, route of delivery, and dose. There is some evidence that transdermal delivery is safer than oral administration.

The approved indications for treating menopausal or postmenopausal women with estrogens are the treatment of menopausal vasomotor symptoms and prevention of postmenopausal osteoporosis.

The main established risks of estrogens are an increased risk of cardiovascular disease, including venous thromboembolism, myocardial infarction, or stroke. It has also been established that there is an increased risk of endometrial cancer when estrogen is given without progestin, that there is an increased risk of breast cancer when estrogen is given with progestin, and that these changes in risk occur with medroxyprogesterone acetate, a 17-hydroxyprogesterone derivative, and norethindrone or norgestrel/levonorgestrel, which are 19-nortestosterone derivatives. However, the lowest doses and durations of treatment with these progestins that are needed to reduce the risk of endometrial cancer, or increase the risk of breast cancer, have not been established.

#### 1.5 Other Relevant Information

Menostar is not approved or marketed in any country.

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#### 2. Clinically Relevant Findings From Chemistry, Biopharmaceutics, Pharmacology and Toxicology, Statistics, and Other Consultant Reviews

The clinically relevant findings from the reviews referred to above are similar to the findings for Climara, considering the dose of E2. There are six doses of Climara, of which the lowest is delivered by the Climara reference patch. The Menostar dose is ½ of the Climara reference patch dose.

For further information, see chemistry review by Dr. Amit Mitra, biopharmaceutics review by Dr. Johnny Lau, pharmacology/toxicology review by Dr. Karen Davis-Bruno, statistical review by Drs. Japo Choudhury and Todd Sahlroot, consult on endometrial effects by Dr. Phill Price, consult on Prescribing Information by Dr. Laura Pincock, consult on Patient Package Insert by Ms. Jeanine Best, and consult on clinical inspection by Ms. Andrea Slavin.

#### 3. Human Pharmacokinetics and Pharmacodynamics

##### 3.1 Pharmacokinetics, Distribution, Metabolism, and Excretion

**Pharmacokinetics.** Menostar was applied to the abdomens of 18 healthy, nonsmoking women, 60-80 years of age,  $\geq 5$  years postmenopausal, with  $E2 \leq 20$  pg/mL, and  $FSH \geq 40$  mIU/mL. Their mean serum E2 concentrations were consistent with steady E2 delivery through the 7-day application period. Arithmetic and geometric means for the pharmacokinetic parameters were similar. The arithmetic means (%CV) were 14.7 pg/ml (37.3) for Cave over time, and 21.7 pg/ml (32.9) for  $C_{max}$ , which occurred at a median of 42 hours after Menostar application. The daily *in vivo* E2 delivery was 14.3 mcg (24.9), for which the geometric mean was 14 mcg (95% CI 12-16).

**Distribution.** Exogenous E2, like endogenous E2 and other estrogens, is widely distributed in the body, and is generally found in higher concentrations in sex hormone target organs (e.g., uterus and breast) than elsewhere. E2 is highly bound to plasma proteins: about 61% to albumin and about 37% to SHBG. E2 stimulates synthesis of SHBG in the liver more after oral administration than transdermal delivery.

Transdermal E2 delivery avoids the first pass through the liver that occurs with oral E2 (or other estrogens), no effect on liver protein synthesis has been observed, and there is less fluctuation of E2 and metabolite levels than with oral administration.

**Metabolism.** E2 is metabolized mainly in the liver and also in the intestines, kidney, skeletal muscles, and target organs (uterus, breast, etc.). E2 metabolism involves the formation of estrone, estriol, catecholestrogens, and their sulfate and glucuronide conjugates, partly by CYP3A and

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CYP4A. Weekly transdermal delivery of E2 provides an E2:estrone ratio of about 1:1, whereas oral administration provides an E2:estrone ratio of about 1:5, due to the first pass through the liver.

**Excretion.** After parenteral administration of <sup>14</sup>C-estradiol or <sup>14</sup>C-estrone, about 50% of the dose is excreted into bile. However, only about 7% of the dose is excreted in feces, whereas more than 80% is excreted in urine, indicating enterohepatic circulation. The urinary excretion includes E2, estrone, estriol, and their glucuronide and sulfate conjugates.

### 3.2 Pharmacodynamics, Drug Interactions, and Effects of Hepatic or Renal Impairment

**Pharmacodynamics.** Postmenopausal women with serum E2 <5 pg/mL have decreased BMD and increased risk of hip or vertebral fractures, and SHBG ≥1 mcg/dL further increases the risk of fractures. RCTs have shown that treating postmenopausal women with estrogens increases BMD and decreases the risks of hip, vertebral, and other osteoporotic fractures. The Climara reference patch was shown to increase BMD in a RCT.

**Drug Interactions.** The drug interactions below may be important.

CYP450 Enzymes. Estrogens are metabolized by CYP450 enzymes, including CYP3A4. The metabolism of E2 in women treated with Menostar may be increased by CYP3A4 inducers, such as Saint John's Wort, carbamazepine, or phenobarbital, and may be decreased by CYP3A4 inhibitors such as itraconazole, ketoconazole, clarithromycin, erythromycin, or grapefruit juice.

Alcohol. Alcohol consumption increases blood levels of estrogens. In a study of postmenopausal women who consumed single doses of alcohol (0.7--.75 g/kg body weight) while receiving E2 by transdermal delivery or oral administration, E2 blood levels increased by 22% in the transdermal group and 300% in the oral group.

Tobacco. Smoking may decrease the availability of E2 at target tissues, apparently by inducing 2-hydroxylation. In a study of postmenopausal women receiving E2 and norethisterone by oral administration, E2 and estrone blood levels were significantly lower in smokers compared with non-smokers. However, in a study of postmenopausal women receiving E2 by a gel, no meaningful changes were seen in E2 or estrone blood levels for smokers compared with non-smokers.

**Effects of Hepatic or Renal Impairment.** E2 is metabolized by the liver and the metabolites estrone and estriol, and their glucuronide and sulfate conjugates, are excreted in urine. Therefore, higher concentrations of E2

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and it's metabolites may be seen in women treated with Menostar who have hepatic or renal impairment, compared to women who do not.

### 4. Description of Clinical Data and Sources

#### 4.1 Overall Data

Reports were submitted for two clinical studies: (1) a Clinical Pharmacology study and (2) a RCT.

The Clinical Pharmacology study was a Phase 1, 7-day, randomized, crossover, open-label, single-center clinical trial. The patients were 18 Caucasian postmenopausal women 60-80 years of age. The study compared Menostar to the Climara reference patch.

The RCT was a Phase 3, 24-month, randomized, placebo-controlled, parallel-group, double-blind, multi-center clinical trial. The patients were 417 postmenopausal women 60-80 years of age, 92.3% Caucasian, 3.1% Asian, 1.9% Black, 0.7% Hispanic, 0.7% Hawaiian/other Pacific Islander, and 1.2% other. The RCT compared Menostar to placebo.

#### 4.2 Table 1. The Clinical Trials

Report No. (Protocol No.)	Investigator(s) (Country) Publication	Start Date (mm/yyyy) Duration of Treatment Completion Status	Study Design Study Phase	Dose Treatment	Number of Subjects Who Received Treatment*	Age Range in Years (Mean) Sex Race	Location of Report Location of Publication Location of CRF Tabulations Location of CRFs
<b>I. CLINICAL PHARMACOLOGY</b>							
<b>I.1 Bioavailability Study</b>							
A08736 (305851)	Morrison D (United States)	05/2002 7 days  Completed	Open-label, randomized, crossover, single-center  Phase 1	1.0 mg E2 transdermal system (3.25 cm <sup>2</sup> )  2.0 mg E2 transdermal system (6.5 cm <sup>2</sup> )	18  18	60-80 (65.9)  18 Females  18 Caucasians	1) a08736.pdf 2) NA 3) define.pdf 4) NA

continued on next page.

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

### 4.3 Marketplace Experience

None.

### 4.4 Literature Review

#### Berlex References.

The literature review by Berlex comprises summaries of 43 individual publications, under the following headings: initiation of estrogen therapy in elderly women, rationale for development of Menostar (estradiol transdermal system), general issues, bone (with subheadings for low dose estrogen, low dose transdermal estrogen, and ultra-low dose estrogen), fracture prevention, vasomotor symptoms, atrophy, and endometrium (with subheadings for low dose estrogen, low dose transdermal estrogen, ultra-low dose estrogen, and hyperplasia).

The Berlex literature review covers important issues, and appears generally adequate, considering that Menostar is qualitatively identical to, and ½ the size, of Climara, an approved and marketed product.

#### Other important references.

Regarding benefits. Hankinson et al. reported in 1995 on measurements of plasma levels of E2 and other sex hormones in postmenopausal women. Using measurements in 3 blood samples from each of 79 healthy postmenopausal women 51-69 years of age, taken over 3 years, they concluded that "for most of these plasma hormones [including E2], a single measurement can reliably categorize average levels over at least a 3 year period in postmenopausal women." (Hankinson SE, Manson JE,

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Spiegelman D, et al. Reproducibility of plasma hormone levels in postmenopausal women over a 2-3 year period. *Cancer Epidemiology, Biomarkers, and Prevention* 1995;4:649-54.)

This is relevant to Menostar because the RCT supporting the NDA was started in January 2000, -- over a year after Cummings et al. reported that the risk of hip or vertebral fractures in postmenopausal women is significantly increased in women with serum E2 <5 pg/ml, and is not consistently related to serum E2 in women with serum E2 ≥5 pg/ml. (Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. *N Engl J Med* 1998; 339:733-8.) Similar results were reported for BMD (Ettinger B, Pressman A, Sklarin P. Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures. *J Clin Endocrinol Metab* 1998;83:2239-43.) (Note: In the RCT, E2 was measured at baseline, 12 months, and 24 months. At baseline, about ½ of the women had E2 ≥5 pg/ml, suggesting that they might not benefit from Menostar treatment. However, no analyses were presented showing BMD response stratified by baseline E2. These were requested and are discussed below.)

Regarding risks. Regarding low-dose estrogen in general, Cushing et al. reported in 1998 that a low dose of conjugated estrogens by oral administration (0.3 mg/day) significantly increased the risk of endometrial cancer, in a population based, case-control study. (Cushing KL, Weiss NS, Voigt LF, et al. Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. *Obstet Gynecol* 1998;91:35-9.

Regarding transdermal estrogen specifically, Scarabin et al. reported in 2003 that estrogens by oral administration increase the risk of venous thromboembolism, but that estrogens by transdermal delivery do not, in a hospital-based, case-control study. The discussion cites plausible biological evidence in support of this observation. This publication appeared in the same month that the Menostar NDA was submitted, and it is not cited in it. (Scarabin P, Oger E, Plu-Bureau G. Differential association of oral and transdermal estrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-32.

## 5. Clinical Review Methods

### 5.1 General

The review was done with focus on the important issues of efficacy and safety. The Clinical Pharmacology study was reviewed in general. The RCT was reviewed in detail, and the results interpreted in the context of my background in this area, and the published literature.

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#### 5.2 Materials Consulted

This review was based on the electronic NDA; the chemistry review by Dr. Amit Mitra, biopharmaceutics review by Dr. Johnny Lau, pharmacology/toxicology review by Dr. Karen Davis-Bruno, statistical review by Drs. Japo Choudhury and Todd Sahlroot; consultations with Dr. Phill Price, Division of Reproductive & Urologic Drug Products, Dr. Laura Pincock, Division of Drug Marketing, Advertising, & Communications, and Ms. Jeanine Best, Division of Surveillance, Research, & Communication Support, Ms. Andrea Slaving, Division of Scientific Investigations; and published literature.

#### 5.3 Evaluation of Data Quality

The data and literature review were evaluated for completeness, internal consistency, and plausibility, in the context of my background in this area, and the published literature. My findings are discussed in the sections of this review that pertain to the data and the literature review.

#### 5.4 Evaluation of Ethics

The ethics evaluation was based on the NDA. For the Clinical Pharmacology study, the NDA says "conducted in the United States under IND 40,928 in compliance with the Institutional Review Board and Informed Consent regulations pursuant to 21 CFR Parts 56 and 50, respectively. (Report No. A09736 for Protocol No. 305851, See Table 1.) For the RCT, the NDA says "The protocol, all amendments, and appropriate patient consent forms were reviewed and approved by a properly constituted Institutional Review Board (IRB).... A list of all IRBs consulted for this study and the name of each chairperson is provided.... This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All aspects of the study were carefully monitored by representatives of Berlex Laboratories, Inc.... An informed consent form.... was reviewed and approved by each site's IRB prior to its use." A sample informed consent form is provided in an Appendix to the Study Report. (Report No. A11926 for Protocol No. 98188, See Table 1.) I think the information above and the consent form for the RCT are acceptable.

#### 5.5 Evaluation of Financial Disclosure

The financial disclosure evaluation was based on the NDA. The forms used are appropriate, and disclose the required information, to the best I can determine. However, I am concerned that: (1) Dr. Bruce Ettinger is 1 of the 3 inventors of Menostar, (2) Dr. Ettinger was a clinical investigator in the RCT (Protocol No. 98188), which was started in 2000 and was not designed to evaluate the efficacy of Menostar according to baseline endogenous

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E2, (3) Dr. Ettinger was principle author of a paper, published in 1998, which reported that "...women with [endogenous] estradiol levels below 5 pg/ml had substantially less BMD at all skeletal sites.." than women with higher levels, and (4) this paper was not referred to in the clinical part of the NDA. (Ettinger B, Pressman A, Sklarin P. Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures. J Clin Endocrinol Metab 1998;83:2239-43.)

It appears to me that the RCT should have been designed to evaluate the efficacy of Menostar according to baseline endogenous E2.

To clarify this issue, I requested that Berlex replicate the main efficacy analyses, after stratifying the Menostar and placebo groups by baseline endogenous E2 <5 pg/ml and  $\geq$ 5 pg/ml. The results are shown in Section 6.2, Tables 6-7.

## 6. Integrated Review of Efficacy and Safety

### 6.1 General Comments

The NDA provides an 8-page "Integrated summary of benefits and risks for Menostar," rather than separate integrated reviews of efficacy and safety. This summary is divided into 5 sections: Introduction, Benefits, Risks, Conclusions, and References. I think the format is appropriate, since the amount of information is small, and will follow it here. Most of the results are from the RCT, in which there were 208 women in the Menostar group and 209 women in the placebo group.

#### **Introduction.**

Efficacy. The Introduction says that "recent well-controlled studies have uniformly shown a linear dose response with clinically beneficial effects occurring at even very low levels of serum estradiol..." and "...epidemiologic studies have found that older postmenopausal women with serum estradiol levels above 10 pg/mL have higher bone density and fewer fractures than women with estradiol levels below 10 pg/mL."

In reviewing the references cited in support of the statements above, I did not find evidence that Menostar could be expected to have similar effects on BMD for women with differing levels of endogenous E2. Instead, I found citation of a report saying that "...women with [endogenous] estradiol levels below 5 pg/ml had substantially less BMD at all skeletal sites..." than women with higher levels. (Ettinger B, Pressman A, Sklarin P. Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures.

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J Clin Endocrinol Metab 1998;83:2239-43.) I interpret this as supporting an hypothesis that Menostar could be expected to increase BMD more for women with low endogenous E2 compared to women with higher BMD. This hypothesis is further supported by another report, from the same study, on the relationship between endogenous E2 and the risk of hip and vertebral fractures. (Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med. 1998;339:733-8). The report by Ettinger et al. on BMD was not referred to in the clinical part of the NDA, although the report by Cummings et al on hip and vertebral fractures was.

Safety. The Introduction says "...advanced age is associated with increased oral drug bioavailability due to a reduction of hepatic drug-metabolizing capacity and decreased first-pass metabolism. Furthermore, a decreased renal clearance may result in an accumulation and prolonged action at the target tissues/organs with the potential of adverse reactions.

#### **Benefits.**

The Benefits section has 3 parts: "prevention of osteoporosis," "vaginal maturation," and "effects on lipids."

Prevention of Osteoporosis. This part briefly describes postmenopausal osteoporosis, and then says "The phase 3 osteoporosis prevention study was conducted to show efficacy...without producing significant endometrial stimulation." The rest of the "prevention of osteoporosis" part briefly summarizes results from the RCT about bone mineral density, fractures, and biochemical markers of bone remodeling.

Vaginal Maturation. This part describes results from the RCT, which showed increased maturation of vaginal epithelium, for the Menostar group compared to the placebo group, as expected.

Effects on Lipids. This part describes results from the RCT, which showed decreases in mean total and mean low-density lipoprotein cholesterol, and increases in mean triglycerides, for the Menostar group compared to the placebo group, as expected.

#### **Risks.**

The Risks section has 3 parts: "endometrial safety," "bleeding/spotting profile," and "adverse events."

Endometrial Safety. This part begins by saying that "Unopposed treatment with standard doses of estrogens increases the incidence of endometrial hyperplasia and the risk of endometrial cancer." I do not know what is

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meant here by "standard doses," especially since the NDA discuss the report by Cushing et al. a low dose of conjugated estrogens by oral administration (0.3 mg/day) significantly increased the risk of endometrial cancer, in a population based, case-control study. (Cushing KL, Weiss NS, Voigt LF, et al. Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. *Obstet Gynecol* 1998;91:35-9.

The part about endometrial safety next describes results from the RCT based on the 178 (85.6%) women in the Menostar group and 163 (78.0%) women in the placebo group who had biopsies at 1 year, and the 169 (81.3%) women in the Menostar group and 155 (74.2%) women in the placebo group who had biopsies at 2 years.

At 1 year, 5.8% of women in the Menostar group and 1.0% of women in the placebo group had endometrial tissue classified as proliferative, and 1% in each group had polyps diagnosed at biopsy. At 2 years, 3.4% of women in the Menostar group and no women in the placebo group had endometrial tissue classified as proliferative, and 1% in the Menostar group and 0.5% in the placebo group had polyps.

Two (1.0%) women in the Menostar group and no women in the placebo group had abnormal endometrial biopsies. Of these 2 women, 1 was a 67-year old woman who, at 2 years, had an endocervical polyp with "atypical stroma/malignant uterine mixed mesenchymal tumor (adenosarcoma) with areas of rhabdomyosarcomatous differentiation." The other was a 63-year old woman who, at 2 years, had atypical endometrial hyperplasia.

The part about endometrial safety concludes by saying "The endometrial biopsy data confirm that the transdermal ultra-low estradiol patch can be used safely without the addition of a progestin." I do not agree, and think that monitoring and potential use of a progestin would be appropriate. (See Section 6.2 and consult on endometrial effects by Dr. Phill Price.)

Bleeding/spotting Profile. This part describes results from the RCT about vaginal bleeding/spotting. For the Menostar group compared to the placebo group, the rates of bleeding/spotting were similar in the first year, and somewhat greater in the second. I think this supports concern about the long-term effects of Menostar on the endometrium. (See Section 6.2 and consult on endometrial effects by Dr. Phill Price.)

Adverse Events. This part describes results from the RCT about AEs. There were no deaths. The rates of AEs at baseline were 3.4% for the Menostar group and 5.3% for the placebo group. During the RCT, the rates were similar for SAEs in general, for SAEs considered possibly related to treatment, and for discontinuations due to AEs. In total, 93.3% of women in

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the Menostar group and 88.5% of women in the placebo group had AEs during the RCT, including 7.7% in the Menostar group and 11.5% in the placebo group with AEs of severe intensity, 49.5% the Menostar group and 47.8% in the placebo group with AEs of moderate intensity, and 36.1% in the Menostar group and 29.2% in the placebo group with AEs of mild intensity. In total, 39.9% of women in the Menostar group and 26.3% of women in the placebo group had AEs considered possibly, probably, or definitely related to treatment. The excess percent of women with any AE, in the Menostar group compared to the placebo group, were in the urogenital system (excess=12.6%) and nervous system (excess=7.3%). (See Section 6.2).

**Conclusions:** The Conclusions section says "Ultra-low estradiol is safe and effective..." and "The estrogen dose...does not lead to a significant stimulation of the endometrium..." I think the RCT supports concluding that Menostar is effective, and leads to meaningful stimulation of the endometrium in some patients. (See Section 6.2.) The prescribing information and patient package insert should describe the AEs.

**References.** There are 5 references, which do not include the report by Ettinger et al. which says that women with [endogenous] estradiol levels below 5 pg/ml had substantially less BMD at all skeletal sites..." than women with higher levels.

## 6.2 Review of Clinical Trials

There were 2 clinical trials: (1) The Clinical Pharmacology study, a Phase 1, 7-day, randomized, crossover, open-label, single center clinical trial. The patients were 18 Caucasian postmenopausal women 60-80 years of age. The study compared Menostar to the Climara reference patch. See Section 3.1 and the Biopharmaceutics review by Dr. Johnny Lau; (2) the RCT, Phase 3, 24-month, randomized, placebo-controlled parallel-group, double-blind, multi-center, clinical trial. The patients were 417 postmenopausal women 60-80 years of age, 92.3% Caucasian, 3.1% Asian, 1.9% Black, 0.7% Hawaiian/other Pacific Islander, and 1.2% other. The RCT compared Menostar to placebo.

### 6.2.1 The Phase 3 Randomized Clinical Trial (RCT)

#### 6.2.1.1 Objectives

Primary Efficacy Objective. The primary efficacy objective was to show superiority for Menostar compared to placebo, for the prevention of osteoporosis in postmenopausal women. The primary variable for this objective was the mean percent change from baseline in lumbar spine

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BMD at the 24-month endpoint (LOCF), as measured by DXA in an AP view of L2-L4.

Primary Safety Objective. The primary safety objective was to show safety for Menostar compared to placebo, for the incidence of endometrial hyperplasia. The primary variable for this objective was the incidence of endometrial hyperplasia in biopsies taken at 12 and 24 months, or any time when medically indicated, and analyzed at the 12-month and 24-month endpoints (LOCF). All endometrial biopsies were read by 2 independent pathologists who were blinded to treatment group and each other's readings. Biopsies with discrepant readings by these 2 were read by a 3<sup>rd</sup> pathologist to provide a final diagnosis.

Secondary variables. The secondary efficacy variables were total hip BMD, biochemical markers of bone metabolism, quality of life, urinary health, and sexual function (See below for further information). The most important secondary efficacy variable was total BMD at the 24-month endpoint (LOCF), as measured by — Data on fractures were also obtained. The secondary safety variables were pap smears, mammograms, adverse events, vital signs, physical examinations, and clinical laboratory tests.

#### 6.2.1.2 Patient Population

Geography and Calendar Time. Patients were recruited at 9 centers in the United States, located in California, Florida (2 sites), Illinois, Iowa, Minnesota, Tennessee, Virginia, and Washington. The first patient was enrolled on 10 Jan 2000 and the last completed the RCT on 23 Nov 2002.

Inclusion criteria. Female; 60-80 years of age; amenorrhea for  $\geq 5$  years; evaluable spine and hip BMD; intact uterus with negative endometrial biopsy or endometrial thickness  $< 4$  mg by vaginal ultrasound, if inadequate tissue at biopsy; signed informed consent.

Exclusion criteria. BMD Z-score  $< -2$  at lumbar spine (AP view, L2-L4) or total hip; known or suspected bone disease (including osteoporosis); history of hypo- or hyperparathyroidism, Paget's disease, osteomalacia, osteogenesis imperfecta, other metabolic bone disease, hypercalcemia, vitamin D deficiency; fracture within past 6 months; history of heart disease (myocardial infarction, coronary artery bypass graft, percutaneous al coronary angioplasty, coronary stenting, angiographic evidence of  $\geq 50\%$  narrowing of  $\geq 1$  coronary arteries); history of stroke or transient ischemic attacks, history of venous thromboembolic disease requiring past or current anticoagulation; uncontrolled hypertension, systolic BP  $\geq 180$  mm Hg or diastolic BP  $\geq 105$  while sitting at rest; triglycerides  $\geq 300$  mg/dL or glucose  $\geq 180$  mg/dL, at baseline while fasting; uncontrolled

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thyroid disorders, initiation or change in dose of thyroid replacement therapy within past 6 months; current significant liver dysfunction or disease; any history of breast or endometrial cancer, or malignant melanoma; known or suspected malignant or pre-malignant disease (excluding basal or squamous skin cancer) within past 10 years; systemic or gynecologic disorder, laboratory or vaginal ultrasound finding that, in the opinion of the investigator, could interfere with the conduct of the study or interpretation of the results; baseline endometrial biopsy showing simple hyperplasia or worse; systemic treatment with fluoride, calcitonin, or bisphosphates at any time; estrogen or progestin therapy (oral, transdermal, intramuscular, intrauterine, or intravaginal) within past 3 months; participation in another study involving administration of an investigational drug within the past month.

Withdrawal Criteria. Development of arterial or venous thromboembolism (including signs or symptoms of stroke, myocardial infarction, retinal arterial obstruction); deep venous thromboembolism; significant rise in BP as determined by the investigator; jaundice, gallbladder disease, clinical hepatitis; breast cancer; endometrial cancer or hyperplasia; prolonged immobilization; non-compliance (<75%); patient decision.

Treatment Failure. Development of a lumbar spine BMD Z-score <-3, or an annualized rate of lumbar spine BMD decrease  $\geq 6\%$  at 12 months or later. Women with treatment failure could continue study drug; however, they were to be informed about their rates of bone loss, and referred to their primary care physicians.

Screening. A total of 717 women were screened, of whom 417 (58.2%) were randomized. Of the 300 women not randomized, some were excluded for more than 1 reason. There were 309 exclusions, as follows: 76 (24.6%) - eligible but refused, did not return, or was not randomized; 73 (23.6%) - no reason provided; 67 (21.7%) - uterus not entered with biopsy instrument; 22 (7.1%) - did not receive placebo or a follow-up procedure, mammogram, or pap smear; 18 (5.8%) - vaginal ultrasound not done; - 50 (16.2%) - ineligible by exclusion criteria.

Randomization and follow-up. Patients were randomized to Menostar or placebo in a 1:1 ratio using a computer generated code. A total of 417 patients were randomized: 208 to Menostar and 209 to placebo. Of these, 17 (8.2%) in the Menostar group and 24 (11.5%) in the placebo group discontinued before completing the RCT. Another 18 (8.7%) in the Menostar group and 24 (11.5%) in the placebo group discontinued study drug prematurely but completed the RCT.

Patients Analyzed. For efficacy, modified intent-to-treat analyses were done using the "Full Analysis Set," which was all patients randomized who

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had at least one measurement for the outcome variable analyzed. Per protocol analyses were done for 185 (88.9%) patients in the Menostar group and 182 (87.1%) patients in the placebo group. The most important analyses were the modified intent-to-treat analyses at the 12-month and 24-month endpoints (LOCF).

#### **6.2.1.3 Calcium and Vitamin D**

All patients in the RCT were provided with supplements of calcium and vitamin D for self-administration. Calcium was provided as 2 Tums® tablets (800 mg of calcium) and 1 Centrum® tablet (162 mg calcium) per day. The Centrum® tablet included 400 IU vitamin D.

#### **6.2.1.4 RCT Conduct, Data Collection, and Data Analysis**

The methods used to conduct the RCT, for data collection, and data analysis were typical for Phase 3 RCTs and appear generally adequate.

Table 2 shows the RCT schedule of events.

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### 6.2.1.5 Results

The results discussed below are for baseline and modified intent-to-treat analyses at the 12-month and 24-month endpoints (LOCF), unless otherwise specified. Per protocol analyses were also done, with similar results.

#### 6.2.1.5.1 Baseline Characteristics

Table 3 shows baseline general characteristics for women in the Menostar group and the placebo group. Patients in the Menostar group and placebo group were similar for age, race, weight, and other baseline characteristics. The two groups were also similar for baseline gynecologic characteristics (See Table 3A).

**Table 3 Baseline General Characteristics**

Variable	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417	p-value*
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 <sup>2</sup> )				
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	

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Variable	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417	p-value*
<b>Alcohol Intake (in past 30 days)</b>				
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)	
<b>Alcohol Intake (drinks per day)</b>				
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	
<b>Calcium Intake (mg per day)</b>				
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.

\*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.

BMD T-score at Baseline	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417
	n (%)	n (%)	n (%)
> -1	60 (28.8)	74 (35.4)	134 (32.1)
≤ -1 to > -2.5	107 (51.4)	107 (51.2)	214 (51.3)
≤ -2.5	41 (19.7)	28 (13.4)	69 (16.6)

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

### 6.2.1.5.2 Efficacy

#### 6.2.1.5.2.1 Main Efficacy Results

The results for BMD refer to measurements by DXA of lumbar spine BMD at L2-L4 and total hip BMD. (See statistical review by Drs. Choudhury and Sahlroot for further information.)

**Main Efficacy Results from Berlex Analyses.** Tables 4-5 show results for lumbar spine BMD, the primary efficacy variable, and total hip BMD, the most important secondary efficacy variable. See Tables 4-5A for details. The text below includes the mean absolute values at baseline.

**Lumbar Spine.** At baseline, mean lumbar spine BMD was 0.936 g/cm<sup>2</sup> in the Menostar group and 0.955 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar increased lumbar spine BMD by a mean of 2.29% compared to a mean increase of 0.51% for placebo, p<0.001. At the 24-month endpoint, Menostar increased lumbar spine BMD by a mean of 2.99% compared to a mean increase of 0.54% for placebo, p<0.001.

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**Total Hip.** At baseline, mean total hip BMD was 0.835 g/cm<sup>2</sup> in the Menostar group and 0.840 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar increased total hip BMD by a mean of 0.90% compared to a decrease of 0.22% for placebo, p<0.001. At the 24-month endpoint, Menostar increased total hip BMD by a mean of 0.84% compared to a mean decrease of 0.71% for placebo, p<0.001.

At both endpoints, larger percentages of patients in the Menostar group compared to the placebo group had no loss in lumbar spine BMD and no loss in total hip BMD, p<0.001 for each comparison.

**Table 4. Mean Percent Change from Baseline in Lumbar Spine and Total Hip**

Mean Percent Change From Baseline in Lumbar Spine and Total Hip BMD (Full Analysis Set)						
Lumbar spine				Total hip		
	Ultra-low Estradiol	Placebo	p-value	Ultra-low Estradiol	Placebo	p-value
	N = 208	N = 209		N = 208	N = 209	
	n = 189	n = 186		n = 189	n = 184	
12-Month Endpoint	2.29	0.51	< 0.001	0.90	-0.22	< 0.001
	n = 189	n = 186		n = 189	n = 185	
24-Month Endpoint	2.99	0.54	< 0.001	0.84	-0.71	< 0.001

N = total number of patients; n = number of patients with data available.

**Table 5. Percent of Patients with No Change in Lumbar Spine and Total Hip BMD**

Percentage of Patients Who Had No Loss in Lumbar Spine and Total Hip BMD (Full Analysis Set)						
Lumbar Spine				Total hip		
	Ultra-low Estradiol	Placebo	p-value	Ultra-low Estradiol	Placebo	p-value
	N = 208	N = 209		N = 208	N = 209	
	n = 189	n = 186		n = 189	n = 184	
12-Month Endpoint	78%	54%	< 0.001	66%	50%	0.001
	n = 189	n = 186		n = 189	n = 185	
24-Month Endpoint	80%	56%	< 0.001	63%	43%	< 0.001

N = total number of patients; n = number of patients with data available.

**Main Efficacy Results from My Analyses.** Tables 6-7 show results from my main efficacy analyses. These were done in the same way as the Berlex main efficacy analyses, except that mine were done separately for patients with baseline (endogenous) E2 <5 pg/mL compared to ≥5 pg/mL. See Tables 6-7A for details. In the text below, I have included the mean absolute values at baseline.

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Lumbar Spine, baseline E2 <5 pg/mL. At baseline, mean lumbar spine BMD was 0.920 g/cm<sup>2</sup> in the Menostar group and 0.938 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar increased lumbar spine BMD by a mean of 2.52% compared to an mean increase of 0.47% for placebo, p<0.001. At the 24-month endpoint, Menostar increased lumbar spine BMD by a mean of 3.50% compared to a mean increase of 0.29% for placebo, p<0.001.

Lumbar Spine, baseline E2 >5 pg/mL. At baseline, mean lumbar spine BMD was 0.954 g/cm<sup>2</sup> in the Menostar group and 0.975 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar increased lumbar spine BMD by a mean of 2.04% compared to an mean increase of 0.55% for placebo, p<0.001. At the 24-month endpoint, Menostar increased lumbar spine BMD by a mean of 2.40% compared to a mean increase of 0.81% for placebo, p<0.001.

Total Hip, Baseline E2 <5 pg/mL. At baseline, mean total hip BMD was 0.822 g/cm<sup>2</sup> in the Menostar group and 0.828 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar increased total hip BMD by a mean of 1.03% compared to a decrease of 0.64% for placebo, p<0.001. At the 24-month endpoint, Menostar increased total hip BMD by a mean of 1.04% compared to a mean decrease of 1.09% for placebo, p<0.001.

Total Hip, Baseline E2 >5 pg/mL. At baseline, mean total hip BMD was 0.850 g/cm<sup>2</sup> in the Menostar group and 0.854 g/cm<sup>2</sup> in the placebo group. At the 12-month endpoint, Menostar increased total hip BMD by a mean of 0.76% compared to a decrease of 0.24% for placebo, p=0.163. At the 24-month endpoint, Menostar increased total hip BMD by a mean of 0.61% compared to a mean decrease of 0.31% for placebo, p=0.045.

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**Table 6. Mean Percent Change from Baseline In Lumbar Spine and Total Hip BMD: Baseline E2 <5 pg/mL Compared to ≥5 pg/mL**

**Patients with Baseline E2 <5 pg/mL**

Lumbar Spine				Total Hip			
	Menostar N= 110	Placebo N= 110	p-value		Menostar N= 110	Placebo N=110	p-value
	n= 101	n= 97			n= 101	n= 96	
<b>12-month Endpoint</b>	<b>2.52</b>	<b>0.47</b>	<b>&lt;0.001</b>	<b>12-month Endpoint</b>	<b>1.03</b>	<b>- 0.64</b>	<b>&lt;0.001</b>
	n= 101	n= 97			N= 101	n= 96	
<b>24-month Endpoint</b>	<b>3.50</b>	<b>0.29</b>	<b>&lt;0.001</b>	<b>24-month Endpoint</b>	<b>1.04</b>	<b>- 1.09</b>	<b>&lt;0.001</b>

**Patients with Baseline E2 ≥5 pg/mL**

Lumbar Spine				Total Hip			
	Menostar N= 98	Placebo N= 99	p-value		Menostar N= 98	Placebo N=99	p-value
	n= 88	n= 89			n= 101	n= 96	
<b>12-month Endpoint</b>	<b>2.04</b>	<b>0.55</b>	<b>0.003</b>	<b>12-month Endpoint</b>	<b>0.76</b>	<b>0.24</b>	<b>0.163</b>
	n= 88	n= 89			N= 101	n= 96	
<b>24-month Endpoint</b>	<b>2.40</b>	<b>0.81</b>	<b>0.002</b>	<b>24-month Endpoint</b>	<b>0.61</b>	<b>- 0.31</b>	<b>0.045</b>

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**Table 7. Percent of Patients with No Loss in Lumbar Spine and Total Hip BMD: Baseline E2 <5 pg/mL Compared to ≥5 pg/mL**

**Patients with Baseline E2 <5 pg/mL**

Lumbar Spine				Total Hip			
	Menostar N= 110	Placebo N= 110	p-value		Menostar N= 110	Placebo N=110	p-value
	n= 101	n= 97			n= 101	n= 96	
<b>12-month Endpoint</b>	<b>79%</b>	<b>54%</b>	<b>&lt;0.001</b>	<b>12-month Endpoint</b>	<b>69%</b>	<b>43%</b>	<b>&lt;0.001</b>
	n= 101	n= 97			N= 101	n= 96	
<b>24-month Endpoint</b>	<b>84%</b>	<b>49%</b>	<b>&lt;0.001</b>	<b>24-month Endpoint</b>	<b>64%</b>	<b>38%</b>	<b>&lt;0.001</b>

**Patients with Baseline E2 ≥5 pg/mL**

Lumbar Spine				Total Hip			
	Menostar N= 98	Placebo N= 99	p-value		Menostar N= 98	Placebo N=99	p-value
	n= 88	n= 89			n= 101	n= 96	
<b>12-month Endpoint</b>	<b>76%</b>	<b>54%</b>	<b>0.002</b>	<b>12-month Endpoint</b>	<b>63%</b>	<b>58%</b>	<b>0.501</b>
	n= 88	n= 89			N= 101	n= 96	
<b>24-month Endpoint</b>	<b>75%</b>	<b>63%</b>	<b>0.090</b>	<b>24-month Endpoint</b>	<b>63%</b>	<b>48%</b>	<b>0.046</b>

#### 6.2.1.5.2.2 Other Efficacy Results

**Bone Mineral Density.** Analyses were done for 3 subgroups of patients based on the "Note for Guidance on Postmenopausal Osteoporosis in Women" issued by the CPMP in January 2001 (CPMP/EWP/552/95 rev 1). These subgroups were defined by osteopenia (BMD T-score for lumbar spine or hip between -2.5 and -1.0) or osteoporosis (both BMD T-scores below -2.5), and additional osteoporosis risk factors (oophorectomy before menopause, early menopause, BMI <20 kg/m<sup>2</sup>, smoking in past 10 years, and alcohol intake more than 20 g (1/2 ounce)/day). The subgroups were-- Subgroup 1: Patients with osteopenia and at least 1 additional risk factor, Subgroup 2: Patients with osteopenia or osteoporosis and at least 1 additional risk factor, Subgroup 3: Patients with osteopenia. Results of the analyses are shown in Table 8. These subgroup definitions were less useful than the analyses by baseline E2 for identifying women in whom Menostar increased mean lumbar spine and total hip BMD.

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**Table 8. Mean Percent Change from Baseline in Lumbar Spine and Total Hip BMD for Subgroups defined by CPMP Guidance**

	Lumbar spine			Total hip		
	Ultra-low Estradiol	Placebo	p-value	Ultra-low Estradiol	Placebo	p-value
<b>Subgroup I</b>	N = 32	N = 26		N = 32	N = 26	
	n = 30	n = 22		n = 30	n = 22	
12-Month Endpoint	1.65	-0.02	NS	1.00	-0.53	NS
	n = 30	n = 22		n = 30	n = 22	
24-Month Endpoint	2.87	0.31	0.018	0.39	-1.00	NS
<b>Subgroup II</b>	N = 52	N = 35		N = 52	N = 35	
	n = 50	n = 30		n = 50	n = 30	
12-Month Endpoint	1.89	0.00	0.022	0.84	-0.26	NS
	n = 50	n = 30		n = 50	n = 30	
24-Month Endpoint	2.36	0.52	0.047	0.23	-0.90	NS
<b>Subgroup III</b>	N = 107	N = 107		N = 107	N = 107	
	n = 95	n = 90		n = 95	n = 88	
12-Month Endpoint	2.53	0.14	<0.001	1.11	-0.58	<0.001
	n = 95	n = 90		n = 95	n = 89	
24-Month Endpoint	3.19	0.43	<0.001	0.83	-1.25	<0.001

N = total number of patients in each treatment group within each subgroup; n = number of patients with data available; NS = not statistically significant.

**Biochemical Markers of Bone Formation and Absorption.** The biochemical markers were serum osteocalcin and serum bone-specific alkaline phosphatase for bone formation, and serum carboxyterminal telopeptide of type 1 collagen and urinary deoxypyridinoline /creatinine ratio for bone absorption. The markers of formation were increased, and the markers of absorption were decreased. The results were statistically significant. See Tables 9-12 in Section 10.

**Quality of Life.** Quality of life was measured with the Medical Outcomes Study 36-Item Health Survey, the Profiles of Mood States, the Center for Epidemiologic Studies Depression Scale (short version), and measurements of urinary health (daytime frequency, nighttime frequency, leaking due to stress or strain, leaking due to urgency and infection), and sexual health (problems and activity). There were no statistically significant or clinically meaningful differences between the Menostar group and the placebo group for these measures of quality of life.

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**Cognitive Function.** Cognitive function was measured with the Modified Min-Mental Status Examination, Logical Memory Test, Logical Memory Delayed Test, Brief Visuospatial Test, Brief Visuospatial Memory Delayed Test, Word List Memory, Work List recall, Trail Making Test B, Modified Boston Naming Test, and Verbal Fluency (category fluency). There were no statistically significant or clinically meaningful differences between the Menostar group and the placebo group for these measures of cognitive function. In both treatment groups, there were statistically significant improvements during the RCT for many of the measures, although these were small, and not considered clinically significant by Berlex. (Data not shown.)

#### 6.2.1.5.3 Safety

The results below include endometrial biopsies, SAEs, and AEs within 60 days after study drug was discontinued.

##### 6.2.1.5.3.1 Extent of Exposure

Table 13 shows the extent of exposure. The mean (minimum, maximum) was 654 days (7, 774) for the Menostar group and 632 days (33, 766) for the placebo group.

**Table 13. Extent of Exposure to Menostar and Placebo**

Statistic	Treatment		Total
	Ultra-low Estradiol	Placebo	
N	208	209	417
Mean (SD)	654 (185)	632 (195)	643 (190)
Median	727	726	727
Minimum	7	33	7
Maximum	774	766	774

N = total number of patients; SD = standard deviation.

##### 6.2.1.5.3.2 Endometrium

Aspiration biopsies of the endometrium were done at baseline, 12 months, and 24 months. Transvaginal ultrasonograms were done if endometrial biopsy did not yield diagnostic tissue or if needed in the judgment of the investigator.

The endometrial biopsy results are also reviewed in the consult on endometrial effects by Dr. Phill Price. All endometrial biopsies were read by 2 independent pathologists in different laboratories, who were blinded to treatment group and each other's readings. When they disagreed, the biopsy was read by another independent pathologist, whose reading was

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considered to resolve the disagreement. The first 2 pathologists disagreed about diagnoses for 23 biopsies. Of these, the disagreement was about normal results for 21 biopsies and abnormal results for 2. In the resolution of these disagreements, 1 biopsy was called abnormal in each treatment group. See Table 14 in Section 10.

**Baseline Endometrial Biopsy Results.** At baseline, all patients had endometrial biopsies except 1 in the Menostar group who had a stenotic cervix. Transvaginal ultrasonograms were done for 43 (20.7%) patients in the Menostar group and 56 (26.8% patients in the placebo group.

Table 15 show results for the baseline endometrial biopsies. See Table 15 A for details and results of the baseline transvaginal ultrasonograms.

**Table 15. Baseline Endometrial Biopsy Results**

Variable	Menostar (N=208) n (%)	Placebo (N=209) n (%)
No biopsy	1 ( 0.5%)	0
Insufficient tissue	42 (20.2%)	53 (25.4%)
Normal	165 (79.3%)	156 (74.6%)
Proliferative endometrium	0	0
Other endometrium*	165 (79.3%)	156 (74.6%)
Polyps	0	0
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium ( n=331)and/or inactive/atrophic endometrium (total n=26)

**12-month and 24-month Endpoint Endometrial Biopsy Results from Berlex Analyses.** See Tables 16-17. Proliferative endometrium was reported at the 12 month endpoint for 12 (5.8%) patients in the Menostar group and 2 (1.0%) patients in the placebo group, and at the 24-month endpoint for 7 (3.4%) patients in the Menostar group and no patients in the placebo group. Normal polyps were reported at the 12-month endpoint for 2 (1.0%) patients in each treatment group, and at the 24-month endpoint for 2 (1.0%) patients in the Menostar group and 1 (0.5%) patient in the placebo group. Abnormal endometrium was reported at the 12-month endpoint for no patients in either treatment group, and at the 24-month endpoint for 1 (0.5%) patient in the Menostar group and no patients in the placebo group. The patient in the Menostar group with abnormal endometrium at the 24-month endpoint had atypical hyperplasia. Another patient had an endocervical polyp with atypical stroma/adenosarcoma. See Tables 16-17.

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**Table 16. 12-month Endpoint Endometrial Biopsy Results**

Variable	Menostar (N=208) n (%)	Placebo (N=209) n (%)
No biopsy	11 ( 5.3%)	25 ( 12.0%)
Insufficient tissue	30 (14.4%)	38 (18.2%)
Normal	148 (71.2%)	125 (59.8%)
Proliferative endometrium	12 ( 5.8%)	2 ( 1.0%)
Other* endometrium	135 (64.9%)	123 ( 58.9%)
Polyps	2 ( 1.0%)	2 ( 1.0%)
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=202)and/or inactive/atrophic endometrium (n=56)

**Table 17. 24-month Endpoint Endometrial Biopsy Results**

Variable	Menostar (N=208) n (%)	Placebo (N=209) n (%)
No biopsy	20 ( 9.6%)	33 (15.8%)
Insufficient tissue	23 ( 11.1%)	31 ( 14.8%)
Normal	156 (75.0%)	136 (65.1%)
Proliferative endometrium	7 ( 3.4%)	0
Other endometrium**	148 (71.2%)	136 (65.1%)
Polyps	2 ( 1.0%)	1 (0.5%)
Abnormal**	1 ( 0.5%)	0
Abnormal, in cervix ***	1 ( 0.5%)	0

\* benign surface/glandular lining epithelium (n=138), inactive/atrophic endometrium (n=144), progestational secretory endometrium (n=1), and menstrual type endometrium (n=1)

\*\* atypical hyperplasia

\*\*\*endocervical polyp with atypical stroma/adenosarcoma

### **12-month and 24-month Endpoint Endometrial Biopsy Results from My Analyses. See Tables 18-19.**

Baseline E2<5 pg/mL. Proliferative endometrium was reported at the 12-month endpoint for 9 (8.2%) patients in the Menostar group and no patients in the placebo group, and at the 24-month endpoint for 2 (1.8%) patients in the Menostar group and no patients in the placebo group. Normal polyps were reported at the 12-month endpoint for 1 (0.9%) patient in the Menostar group and 2 (1.8%) patients in the placebo group, and at the 24-month endpoint for 2 (1.8%) patients in the Menostar group and 1 (0.9%) patient in the placebo group. Abnormal endometrium was not reported.

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Baseline E2 >5 pg/mL. Proliferative endometrium was reported at the 12-month endpoint for 3 (3.1%) patients in the Menostar group and 2 (2.0%) patients in the placebo group, and at the 24-month endpoint for 5 (5.1%) patients in the Menostar group and no patients in the placebo group. Normal polyps were reported for at the 12-month endpoint for 1 (1.0%) patient in the Menostar group and no patients in the placebo group, and at the 24-month endpoint for no patients in either treatment group. Abnormal endometrium was reported at the 12-month endpoint for no patient in either treatment group, and at the 24-month endpoint for 1 (1.0%) patient in the Menostar group and no patients in the placebo group. The patient in the Menostar group with abnormal endometrium at the 24 month-month endpoint had atypical hyperplasia.

**Table 18. 12-month Endpoint Endometrial Biopsy Results**

#### Patients with Baseline E2 <5 pg/mL

Variable	Menostar (N=110) n (%)	Placebo (N=110) n (%)
No biopsy	4 ( 3.6%)	14 (12.7%)
Insufficient tissue	15 (13.6%)	21 (19.1%)
Normal	83 (75.5%)	64 (58.2%)
Proliferative endometrium	9 ( 8.2%)	0
Other* endometrium	73 (66.4%)	64 (58.2%)
Polyps	1 (0.9%)	2 (1.8%)
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=113)and inactive/atrophic endometrium (n=24)

#### Patients with Baseline E2 ≥5 pg/mL

Variable	Menostar (N=99) n (%)	Placebo (N=98) n (%)
No biopsy	7 ( 7.1%)	11 (11.1%)
Insufficient tissue	15 (15.3%)	17 (17.2%)
Normal	65 (66.3%)	61 (61.6%)
Proliferative endometrium	3 ( 3.1%)	2 ( 2.0%)
Other* endometrium	62 (63.3%)	59 (59.6%)
Polyps	1( 1.0%)	0
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=89)and inactive/atrophic endometrium (n=32)

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**Table 19. 24-month Endpoint Endometrial Biopsy Results**

**Patients with Baseline E2 <5 pg/mL**

Variable	Menostar (N=110) n (%)	Placebo (N=110) n (%)
No biopsy	8 ( 7.3%)	17 (15.5%)
Insufficient tissue	14 (12.7%)	13 (11.8%)
Normal	84 (76.4%)	74 (67.3%)
Proliferative endometrium	2 ( 1.8%)	0
Other endometrium*	81 (73.6%)	74 (67.3%)
Polyps	2 ( 1.8%)	1 ( 0.9%)
Abnormal	0	0
Abnormal, in cervix**	1 ( 0.9%)	

\* benign surface/glandular lining epithelium (total n=81) and inactive/atrophic endometrium (total n=74)

\*\*endocervical polyp with atypical stroma/adenosarcoma

**Patients with Baseline E2 ≥5 pg/mL**

Variable	Menostar (N=98) n (%)	Placebo (N=99) n (%)
No biopsy	12 (12.2%)	16 (16.2%)
Insufficient tissue	9 ( 9.2%)	18 (18.2%)
Normal	72 (73.5%)	62 (62.6%)
Proliferative endometrium	5 ( 5.1%)	0
Other endometrium*	67 (68.4%)	62 (62.6%)
Polyps	0	0
Abnormal**	1 ( 1.0%)	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=57), inactive/atrophic endometrium (n=70), progesterational/secretory endometrium (n=1), and menstrual type endometrium (n=1)

\*\*atypical hyperplasia

Further review showed that only 2 patients had endometrial proliferation at both the 12-month and 24-month endpoint biopsies, both in the Menostar group. Also, at 12 months and 24-months, mean E2 levels were similar for patients with endometrial proliferation who had baseline E2 levels <5 pg/mL compared to ≥5 pg/mL.

#### 6.2.1.5.3.3 Adverse Events (AEs)

See Table 2 for schedule of evaluation.

**Deaths.** There were no deaths.

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**Serious Adverse Events (SAEs).** There were 24 (11.5%) patients in the Menostar group and 23 (11.0%) patients in the placebo group with SAEs. There were no meaningful differences between the two groups. See Table 20 in Section 10.

**Discontinuations due to AEs.** There were 21 (10.1%) patients in the Menostar group and 21 (10.0%) patients in the placebo group who discontinued study drug due to AEs. This included no patients in the Menostar group and 4 (1.9%) patients in the placebo group who discontinued due to osteoporosis. There were no other meaningful differences between the two groups. See Table 21 in Section 10.

**Any AE.** There were 194 (93.3%) patients in the Menostar group and 185 (88.5%) patients in the placebo group with any AE. Table 22 shows these by body system. Further review by type of AE (Preferred Term) showed meaningful differences between the Menostar group and the placebo group only in the Urogenital System. See Table 23 below. There was a potentially meaningful difference in the Nervous System that was not meaningful on further review. See Table 24 in Section 10.

**Table 22. Any AE, by Body System**

Body System	Treatment	
	Ultra-low estradiol N = 208 n (%)	Placebo N = 209 n (%)
Number (%) of patients with at least 1 adverse event	194 (93.3)	185 (88.5)
Body as a Whole	102 (49.0)	106 (50.7)
Cardiovascular System	32 (15.4)	34 (16.3)
Digestive System	63 (30.3)	60 (28.7)
Endocrine System	7 (3.4)	5 (2.4)
Hemic and Lymphatic System	8 (3.8)	7 (3.3)
Injection Reactions	0 (0.0)	1 (0.5)
Metabolic and Nutritional Disorders	33 (15.9)	30 (14.4)
Musculoskeletal System	58 (27.9)	53 (25.4)
Nervous System	53 (25.5)	38 (18.2)
Respiratory System	68 (32.7)	72 (34.4)
Skin and Appendages	62 (29.8)	65 (31.1)
Special Senses	24 (11.5)	24 (11.5)
Urogenital System	82 (39.4)	56 (26.8)

N = total number of patients; n = number of patients with data available.

This table includes all adverse events with a start date that occurred on or after study treatment date with the following exception: Adverse events with start date after the last study day are not included.

Patients with more than 1 occurrence of same adverse event were counted once.

**Urogenital System.** Table 23 shows the Urogenital System AEs. According to the investigators, there were 3 (1.4%) patients in the Menostar group and 1 (0.5%) patient in the placebo group with severe

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AEs, 20 (9.6%) patients in the Menostar group and 17 (8.1%) patients in the placebo group with moderate AEs, and the rest had mild AEs. The types of severe AEs (Preferred Terms) were Cervical Neoplasm, Uterine Disorder, and Vulvovaginal Disorder in the Menostar group, and Uterine Disorder in the placebo group. The Investigators' Terms for these AEs were Epithelial Abnormality/Endocervical Mass, Severe Uterine Prolapse, and Vaginal Itching for the patients in the Menostar group, and Worsening Uterine Prolapse/Symptomatic for the patient in the placebo group. The patient with Vaginal Itching recovered without treatment. The Epithelial Abnormality/Endocervical Mass was found at endometrial biopsy on the last visit and was the adenocarcinoma shown in Table 19. . "This malignant tumor is not associated with estrogen therapy and probably arose de novo." See consult on endometrial effects by Dr. Phill Price.

There were 13 (6.3%) patients in the Menostar group and 4 (1.9%) patients in the placebo group with Cervical Neoplasm, and 22 (10.6%) patients in the Menostar group and 3 (1.4%) patients in the placebo group with Leukorrhea, as the types of AEs (Preferred Terms). There were no meaningful differences between the two groups for other Urogenital System AEs. The increase in leukorrhea was expected.

Of the 17 patients with Cervical Neoplasm as the type of AE (Preferred Term), all had endocervical polyps except 1 in the placebo group with a cervical cyst (1 in the Menostar group had a "possible" endocervical polyp). All of these 17 patients were biopsied at 12 and/or 24 months, except 1 in the Menostar group. Of the 16 patients biopsied, 1 patient in the Menostar group had the endocervical polyp with atypical stroma/adenocarcinoma shown in Table 19. The other 15 patients in the Menostar group, and the 4 patients in the placebo group, had biopsies showing "strip of benign surface & glandular lining epithelium," "inactive/atrophic endometrium," or "tissue insufficient for diagnosis."

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**Table 23. Urogenital System: Any AE**

Body System / Preferred Term	E2 Ultralow (N=208) n(%)	Placebo (N=209) n(%)
Urogenital System	82 (39.4)	66 (28.8)
Cervicitis	3 (1.4)	1 (0.5)
Cervix carcinoma	0 (0.0)	1 (0.5)
Cervix disorder	6 (2.9)	6 (2.9)
Cervix neoplasia	13 (6.3)	4 (1.9)
Cystitis	4 (1.9)	1 (0.5)
Dysuria	2 (1.0)	0 (0.0)
Endometrial disorder	2 (1.0)	0 (0.0)
Endometrial hyperplasia	1 (0.5)	0 (0.0)
Endometrial neoplasia	3 (1.4)	0 (0.0)
Female genital pain	1 (0.5)	0 (0.0)
Genital leukoplakia	0 (0.0)	1 (0.5)
Hematuria	2 (1.0)	2 (1.0)
Kidney calculus	1 (0.5)	0 (0.0)
Labial edema	1 (0.5)	0 (0.0)
Leukorrhea	22 (10.6)	3 (1.4)
Ovarian Cyst	1 (0.5)	1 (0.5)
Ovarian disorder	1 (0.5)	1 (0.5)
Papanicolaou smear suspicious	4 (1.9)	4 (1.9)
Proteinuria	0 (0.0)	1 (0.5)
Pyuria	0 (0.0)	1 (0.5)
Salpingitis	1 (0.5)	0 (0.0)
Urinary incontinence	2 (1.0)	1 (0.5)
Urinary tract disorder	2 (1.0)	0 (0.0)
Urinary tract infection	18 (8.7)	19 (9.1)
Urinary urgency	0 (0.0)	1 (0.5)
Urine abnormality	2 (1.0)	3 (1.4)
Urogenital disorder	1 (0.5)	1 (0.5)
Urogenital neoplasia	0 (0.0)	1 (0.5)
Uterine disorder	7 (3.4)	2 (1.0)
Uterine fibroids degenerated	0 (0.0)	1 (0.5)
Uterine hemorrhage	1 (0.5)	0 (0.0)
Uterine neoplasia	0 (0.0)	1 (0.5)
Vaginal Dryness	0 (0.0)	1 (0.5)
Vaginal hemorrhage	7 (3.4)	4 (1.9)
Vaginal moniliasis	3 (1.4)	0 (0.0)
Vaginitis	2 (1.0)	1 (0.5)
Vulvovaginal disorder	6 (2.4)	3 (1.4)
Vulvovaginitis	1 (0.5)	0 (0.0)

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 This table includes all adverse events with a start date that occurred on or after study treatment date with the following exception: Adverse events with start date after the last study day are not included. Subjects with more than one occurrence of same adverse event were counted once.

### 6.2.1.5.3.4 Clinical Laboratory

Results were reviewed for baseline and modified intent-to-treat analyses at 24 months or the last visit, except for the hormone levels, where review included results at 12 months. This was done for mean, median, minimum, and maximum absolute levels, and for mean, median, minimum, and maximum absolute changes from baseline. This was also done for shift tables, which used categories of low, normal, high, or not done, at baseline, 12 months, and 24 months or the last visit.

**Hematology.** The hematology variables were hemoglobin, hematocrit, erythrocyte count, leukocyte count, platelet count, and percents for bands, neutrophils, basophils, eosinophils, lymphocytes, and monocytes. There were no meaningful differences between treatment groups at 24 months or the last visit.

**Blood Chemistry.** The blood chemistry variables were gamma-glutamyl transferase, aspartamine aminotransferase, alanine aminotransferase,

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total bilirubin, lactate dehydrogenase, total protein, albumin, urea nitrogen, creatinine, uric acid, calcium, phosphorous, sodium, potassium, chloride, and thyroid stimulant hormone. There were no meaningful differences between treatment groups at 24 months or the last visit.

**Urinalysis.** The urinalysis variables were pH, glucose, ketones, blood, and protein by dipstick. Leukocytes/high power field were also evaluated. There were no meaningful differences between treatment groups at 24 months or the last visit.

**Blood Lipids.** The blood lipid variables were total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total cholesterol/high-density lipoprotein cholesterol ratio. There were no meaningful differences between treatment groups at 24 months or the last visit.

**Plasma Hormones.** The plasma hormone variables were estrone, estradiol, and sex hormone binding globulin. The only meaningful difference between treatment groups was the expected increase in E2 levels in the Menostar group. See Table 25 in Section 10.

#### 6.2.1.5.3.5 Vital Signs

Results were reviewed for baseline and modified intent-to-treat analyses at 4 month intervals and the 12-month and 24-month endpoints. This was done for mean, median, minimum, and maximum absolute levels, and for mean, median, minimum, and maximum changes from baseline to the intervals and endpoints. The NDA presents results for systolic and diastolic blood pressure. Radial pulse was evaluated but results were presented. There were no meaningful differences between treatment groups.

#### 6.2.1.5.3.6 Physical Examinations.

Results were reviewed for baseline and modified intent-to-treat analyses at 12 months and 24 months or the last visit. This was done for shift tables, which used categories of normal, abnormal, or not done. Under Pelvic, there were 29 (15.3%) patients in the Menostar group and 17 (9.0%) patients in the placebo group with results that were normal at baseline and abnormal at 24 months or the last visit, and there were 8 (4.2%) patients in the Menostar group and 12 (6.4%) patients in the placebo group with results that were abnormal at baseline and normal at 24 months or the last visit. The 29 patients with results under Pelvic that were normal at baseline and abnormal at 24 month or the last visit had endocervical polyps (10 patients) hemorrhoids, (5 patients), and other disorders (<5 patients each). Endocervical polyp appears to account for the difference, as discussed above.

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There were no meaningful differences between treatment groups for other categories (head and neck, abdomen, lymph nodes, etc.)

#### **6.2.1.5.3.7 Height, Weight, and BMI**

Results were reviewed for the 12-month and 24-month endpoints. This was done for mean values. There were no meaningful differences between treatment groups.

#### **6.2.1.5.3.8 Mammograms**

Results were reviewed for 12 months and 24 months or the last visit. This was done for shift tables, which used categories of normal, abnormal, or not done. There were no meaningful differences between treatment groups.

#### **6.2.1.5.3.9 Fractures**

According to the protocol, fractures confirmed by X-ray were reported as AEs. In the NDA Table of AEs, there were 4 (1.9%) patients in the Menostar group and 7 (3.3%) patients in the placebo group with "Bone Fracture (Not Spontaneous) as the type (preferred term) of AE, and no other types of fracture. See Table 28 in Section 10. However, the text of the NDA says there were 4 (1.9%) patients in the Menostar group and 10 (4.8%) patients in the placebo group with fractures. I asked Berlex for clarification and was sent a report saying that 3 patients in the placebo group who had fractures were not included in the NDA Table of AEs, including 2 with spontaneous fractures and 1 with a fracture that was found 10 weeks after study drug was discontinued.

#### **6.2.1.5.3.10 Cervix**

Results were reviewed for 12 months and 24 months or the last visit. This was done for shift tables, which used categories for pap smears of normal, benign, or abnormal, for maturation index of mature, indeterminate, immature, or not done, and for maturation value of low, moderate, high, or not done. For maturation value, this was also done for mean, median, minimum, and maximum values.

**Pap Smears.** There were no meaningful differences between treatment groups.

**Maturation Index and Maturation Value.** The results showed decreased immaturity and increased maturation, as expected. See Tables 26 and 27 in Section 10.

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#### 6.2.1.5.3.11 Vaginal Bleeding

Bleeding and spotting were recorded on diary cards. Results were reviewed for 90 day intervals and endpoint (LOCF). This was done for the percentage (95% CI) of patients with no bleeding or spotting in each interval and at endpoint, the number of patients by number of bleeding or spotting episodes in each interval and at endpoint, and the mean, median, maximum, and minimum number of days per bleeding or spotting episode in each interval and at endpoint.

The cumulative percentages of patients with no bleeding or spotting at endpoint were 89% (95% CI 85%-93%) in the Menostar group and 96% (95% CI 94%-98%) in the placebo group. For the Menostar group minus the placebo group, the mean percentages of patients with no bleeding or spotting, by interval, were in the range of 0-4% for all intervals through 540 days, 6% for the 541-630 day interval, and 10% for the 631-730 day interval.

In the last 2 intervals, the numbers of patients by number of bleeding or spotting episodes in either or both intervals were: in the Menostar group, 18 with 1 episode, 8 with 2-4 episodes, and 1 with 9 episodes; in the placebo group, 4 with 1 episode and 1 with 3 episodes. The longest episodes were 12 days in the Menostar group and 2 days in the placebo group.

### 6.3 Conclusions

The population of postmenopausal women in the RCT was sufficiently representative of Caucasian postmenopausal women about 60 years of age or older to support labeling for this group. There were few women in other racial/ethnic groups.

Menostar is effective for the prevention of osteoporosis in postmenopausal Caucasian women, as measured by increases in lumbar spine and hip BMD, and related changes biochemical markers of bone metabolism. Menostar is probably also effective in postmenopausal women of other racial/ethnic groups, although this has not been shown in a randomized clinical trial. Menostar is more effective for preventing osteoporosis in postmenopausal women in those with lower compared to higher levels of endogenous E2 before treatment.

Menostar does not affect quality of life or cognitive function as measured.

Menostar is safe. However, Menostar™ causes endometrial proliferation in some women, which could increase the risk of hyperplasia or carcinoma. *"It is recommended that class labeling for estrogen and*

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*estrogen/ progestin products be adopted for Menostar.™* If the sponsor elects not to use estrogen class labeling, all bleeding should be investigated by biopsy and all patients should be biopsied at yearly intervals until long term safety data is obtained showing no proliferative effect on the endometrium." "If any proliferation is demonstrated with biopsy, that patient should be treated with a progestin." See consult on endometrial effects by Dr. Phill Price.

#### 7. **Dosing, Regimen, and Administration Issues**

None.

#### 8. **Use in Special Populations**

##### 8.1 **Gender Effects**

Not applicable.

##### 8.2 **Age, Race, or Ethnicity Effects**

Menostar is effective for the prevention of osteoporosis in postmenopausal Caucasian women, as measured by increases in lumbar spine and hip BMD, and related changes biochemical markers of bone metabolism. Menostar is probably also effective in postmenopausal women of other racial/ethnic groups, although this has not been shown in a randomized clinical trial.

##### 8.3 **Effects in Children**

Not Applicable.

##### 8.4 **Data Needed for Special Populations**

The marketplace experience with Climara is an appropriate source of information regarding the adverse events associated with the use of Menostar by postmenopausal women in racial/ethnic groups other than Caucasian.

#### 9. **Conclusions and Recommendations**

##### 9.1 **Conclusions**

Menostar is effective for the prevention of osteoporosis in postmenopausal Caucasian women, as measured by increases in lumbar spine and hip BMD, and related changes biochemical markers of bone metabolism. Menostar is probably also effective in postmenopausal women of other

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racial/ethnic groups, although this has not been shown in a randomized clinical trial. Menostar is more effective for preventing osteoporosis in postmenopausal women in those with lower compared to higher pre-treatment levels of endogenous E2.

Menostar is safe. However, Menostar™ causes endometrial proliferation in some women, which could increase the risk of hyperplasia or carcinoma. *"It is recommended that class labeling for estrogen and estrogen/progestin products be adopted for Menostar.™ If the sponsor elects not to use estrogen class labeling, all bleeding should be investigated by biopsy and all patients should be biopsied at yearly intervals until long term safety data is obtained showing no proliferative effect on the endometrium."* *"If any proliferation is demonstrated with biopsy, that patient should be treated with a progestin."* See consult on endometrial effects by Dr. Phill Price.

#### 9.2 Recommendations

Approve.

Request that Berlex revise labeling to: (1) show efficacy in the RCT separately for women with baseline E2 <5 pg/mL and ≥5 pg/mL; (2) either provide class labeling for estrogen and estrogen/progestin drug products, or state that all bleeding should be investigated by endometrial biopsy, that all patients should be biopsied at yearly intervals until long-term results show no proliferative effect on the endometrium, and that, if any is proliferation found at biopsy, the patient should be treated with a progestin; (3) be consistent with the labeling for Climara, except where there are specific differences for Menostar.

Optional phase 4 study to further evaluate benefits and risks according to levels of endogenous estrogen before treatment and in races/ethnic groups other than Caucasian. This could include studying ways to minimize the need to use progestin for endometrial safety.

#### 10. Tables & Appendices (all referred to in text)

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**Table 1. The Clinical Trials**

Report No. (Protocol No.)	Investigator(s) (Country) Publication	Start Date (mm/yyyy) Duration of Treatment Completion Status	Study Design Study Phase	Dose Treatment	Number of Subjects Who Received Treatment*	Age Range in Years (Mean) Sex Race	Location of Report Location of Publication Location of CRF Tabulations Location of CRFs
<b>1. CLINICAL PHARMACOLOGY</b>							
<b>1.1 Bioavailability Study</b>							
A08736 (305851)	Morrison D (United States)	05/2002  7 days  Completed	Open-label, randomized, crossover, single-center   Phase I	1.0 mg E2 transdermal system (3.25 cm <sup>2</sup> )   2.0 mg E2 transdermal system (6.5 cm <sup>2</sup> )	18   18	60-80 (65.9)  18 Females  18 Caucasians	1) a08736.pdf 2) NA 3) define.pdf 4) NA
<b>2. INDICATION - PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS</b>							
<b>2.1 Controlled Clinical Study With Case Report Forms Available</b>							
A11926 (98188)	Barbier S	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 <sup>2</sup> )   Placebo transdermal system (3.25 cm <sup>2</sup> )	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) crfloc.pdf
	(All study centers were located in the United States.)						
	NA						

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**Table 2. RCT Schedule of Events**

STUDY ENDPOINTS	Screening <sup>a</sup>	Baseline	Pre-treatment Month 1	Visit 1 Month 4	Visit 2 Month 8	Visit 3 Month 12	Visit 4 Month 16	Visit 5 Month 20	Visit 6 <sup>b</sup> Month 24
Medical and Aesthetic History	X								X
Physical Exam including Height, Weight, Blood Pressure and Heart Rate	X								X
Pre-Screening Questionnaire	X								X
Visit Signage		X		X	X	X	X	X	X
Alamogordo <sup>c</sup>	X								X
Alamogordo Study Protocol/Investigator	X								X
Consent and Estimated Costs and Benefits	X								X
Estrogen and Estrogen Levels and SHBG	X					X			X
FSH Screening	X								X
Assessment of Patient Tolerability	X								X
Bone Densitometry of Spine (at 90° view L1-L4), Total Hip (areal)		X				X			X
Serum Osteocalcin, KtP, Bone-Specific Alkaline Phosphatase, Urinary Deoxyphosphonate		X				X			X
ADAM-5, Serum Estradiol, SHBG, Testosterone Free (TFS, DUO)		X		X		X			X
Adverse Event / Tolerability assessment recording			X	X	X	X	X	X	X
Qualitative Feedback Assessments		X		X	X	X	X	X	X
Qualitative Feedback		X		X	X	X	X	X	X
Medication Discontinuation		X		X	X	X	X	X	X
2-Month Survey			X	X	X	X	X	X	X
Prey Data Assessment and Safety Monitoring questionnaire			X	X	X	X	X	X	X

<sup>a</sup>Screening should not take place until the patient has been off estrogen replacement therapy for at least 2 months and may, for logistical reasons, be performed at more than 1 visit. There will be no more than 6 weeks between screening and baseline.

<sup>b</sup>Height was measured at baseline, and Visits 1 through 6.

<sup>c</sup>If the patient was prematurely withdrawn from the study, all the evaluations described under Visit 6 must be performed at the Final Visit.

<sup>d</sup>If a negative mammography has been reported 6 months prior to visit, (provided the report was available) it was not necessary to be repeated at screening.

<sup>e</sup>Optional

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**Table 3. Baseline General Characteristics**

Variable	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417	p-value*
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 <sup>2</sup> )				
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)

Variable	Ultra-low Estradiol N = 208	Placebo N = 209	Total N = 417	p-value*
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.

\*Treatment effect P-values for continuous data are obtained from an ANCOVA 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.

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**Table 3A. Baseline Gynecological Characteristics**

Variable	Statistics	Ultra-low Estradiol 208	Placebo 209	Total 417
Age at First Menstrual Period (years)	N			
	n	208	209	417
	Mean (SD) Minimum-Maximum	12.9 (1.6) 9-19	13.1 (1.6) 9-18	13.0 (1.6) 9-19
Ever been Pregnant?	n	208	209	417
	Yes	190 (91.3)	196 (93.8)	386 (92.6)
	No	18 (8.7)	13 (6.2)	31 (7.4)
	Don't know	0 (0)	0 (0)	0 (0)
	Refused	0 (0)	0 (0)	0 (0)
No. of Pregnancies Resulting in Birth	n	190	196	386
	Mean (SD) Minimum-Maximum	3.2 (1.7) 0-9	3.3 (1.8) 0-11	3.2 (1.7) 0-11
Age at the First Child Born (years)	n	186	193	379
	Mean (SD) Minimum-Maximum	23.6 (4.4) 16-40	23.7 (4.0) 17-38	23.6 (4.2) 16-40
Age at Last Natural Menstruation (years)	n	208	209	417
	Mean (SD) Minimum-Maximum	49.9 (4.7) 28-59	50.5 (4.6) 38-61	50.2 (4.6) 28-61
Hysterectomy?	n	208	209	417
	Yes	0 (0)	0 (0)	0 (0)
	No	208 (100.0)	209 (100.0)	417 (100.0)
	Don't know	0 (0)	0 (0)	0 (0)
	Refused	0 (0)	0 (0)	0 (0)

(continued)

Variable	Statistics	Ultra-low Estradiol 208	Placebo 209	Total 417
Ovary Removed?	N			
	n	208	209	417
	Yes	7 (3.4)	5 (2.4)	12 (2.9)
	No	201 (96.6)	204 (97.6)	405 (97.1)
	Don't know	0 (0)	0 (0)	0 (0)
No. of Ovaries Removed	n	7	5	12
	1	7 (3.4)	5 (2.4)	12 (2.9)
	2	0 (0)	0 (0)	0 (0)
	Don't know	0 (0)	0 (0)	0 (0)
Age when 1 Ovary Removed (years)	n	7	5	12
	Mean (SD) Minimum-Maximum	27.3 (11.6) 16-50	38.6 (14.5) 22-54	32.0 (13.5) 16-54

N = total number of patients; n = number of patients with data available; SD = standard deviation.

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### Tables 4-5. Main Efficacy Results in Berlex Analyses

**Table 4. Mean Percent Change from Baseline in Lumbar Spine and Total Hip BMD**

<b>Mean Percent Change From Baseline in Lumbar Spine and Total Hip BMD (Full Analysis Set)</b>						
<b>Lumbar spine</b>				<b>Total hip</b>		
	<b>Ultra-low Estradiol</b>	<b>Placebo</b>	<b>p-value</b>		<b>Ultra-low Estradiol</b>	<b>Placebo</b>
	<b>N = 208</b>	<b>N = 209</b>			<b>N = 208</b>	<b>N = 209</b>
	<b>n = 189</b>	<b>n = 186</b>			<b>n = 189</b>	<b>n = 184</b>
<b>12-Month Endpoint</b>	2.29	0.51	< 0.001	<b>12-Month Endpoint</b>	0.90	-0.22
					< 0.001	
	<b>n = 189</b>	<b>n = 186</b>		<b>24-Month Endpoint</b>	<b>n = 189</b>	<b>n = 185</b>
<b>24-Month Endpoint</b>	2.99	0.54	< 0.001	<b>24-Month Endpoint</b>	0.84	-0.71
					< 0.001	

N = total number of patients; n = number of patients with data available

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Table 4A. Lumbar Spine BMD: Details of Main Efficacy Results in Berlex Analyses

Table 16: Change and Percent Change From Baseline in Bone Mineral Density (g/cm<sup>2</sup>) of Lumbar Spine (AP View, L2-L4) by Treatment Group and Visit - Full Analysis Set

Treatment (N=208)	Statistics	Visit 3/Month 12		Visit 6/Month 24		12-Month Endpoint (2)		24-Month Endpoint (2)	
		Change	% Change	Change	% Change	Change	% Change	Change	% Change
EZ ultra-low	n	187	187	173	173	188	188	188	188
	Mean	0.021	2.280	0.028	3.048	0.021	2.282	0.027	2.350
	Median	0.020	2.193	0.031	3.220	0.020	2.193	0.020	3.180
	SD	0.0289	3.1042	0.0362	3.5992	0.0288	3.0581	0.0358	3.8884
	Minimum	-0.062	-6.724	-0.080	-6.381	-0.082	-6.724	-0.080	-6.724
	Maximum	0.086	10.302	0.142	20.126	0.086	10.302	0.142	20.126
Placebo (N=209)	n	182	182	180	180	188	188	188	188
	Mean	0.005	0.575	0.007	0.748	0.005	0.509	0.005	0.541
	Median	0.003	0.273	0.005	0.470	0.002	0.156	0.005	0.403
	SD	0.0299	3.2320	0.0334	3.6017	0.0300	3.2488	0.0339	3.8818
	Minimum	-0.092	-9.358	-0.074	-8.371	-0.082	-8.358	-0.082	-8.358
	Maximum	0.094	11.991	0.120	13.180	0.094	11.991	0.120	13.180
	P-value (1)					<0.001	<0.001	<0.001 (3)	<0.001 (3)

Table 17: Proportion of Subjects With No Loss (Change >= D) in Lumbar Spine (AP View L2-L4) Bone Mineral Density - Full Analysis Set

Treatment	Statistics	Visit 3/Month 12	Visit 6/Month 24	12-Month Endpoint (2)	24-Month Endpoint (2)
EZ ultra-low (N=208)	n	187	173	188	188
	Change >= 0	146 (78%)	137 (79%)	147 (78%)	161 (86%)
	Lower	72%	73%	72%	74%
	Upper	84%	85%	84%	85%
Placebo (N=208)	n	182	180	188	188
	Change >= 0	100 (55%)	89 (50%)	100 (54%)	104 (56%)
	Lower	48%	46%	47%	48%
	Upper	82%	85%	87%	85%
	P-value (1)			<0.001	<0.001
	Odds ratio			3.03	3.20
	95% C.I. for odds ratio			(1.98, 4.84)	(2.02, 5.15)

(1) P-values are for between-treatment group comparisons. Default ANCOVA model has terms for treatment, center, and baseline as a covariate. (2) - response rank transformed; (3) - baseline omitted; (4) - treatment by center interaction added.  
 (2) Represents the last observed post baseline value (at that timepoint) carried forward.  
 Lower and Upper refer to the 95% lower and upper asymptotic confidence limits for a single proportion.  
 Only subjects who had evaluations at both baseline and the specified time point are included.  
 (1) P-value, odds ratio, and confidence interval are for between-treatment group comparisons computed from a logistic regression model with terms for treatment and center.  
 (2) Represents the last observed post baseline value (at that timepoint) carried forward.

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**Table 5. Percent of Patients with No Change in Lumbar Spine and Total Hip BMD**

Percentage of Patients Who Had No Loss in Lumbar Spine and Total Hip BMD (Full Analysis Set)							
Lumbar Spine			Total hip				
	Ultra-low Estradiol N = 208	Placebo N = 209	p-value		Ultra-low Estradiol N = 208	Placebo N = 209	p-value
	n = 189	n = 186			n = 189	n = 184	
12-Month Endpoint	78%	54%	<0.001	12-Month Endpoint	66%	50%	0.001
	n = 189	n = 186			n = 189	n = 185	
24-Month Endpoint	80%	56%	<0.001	24-Month Endpoint	63%	43%	<0.001

N = total number of patients; n = number of patients with data available.

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**Table 5A. Total Hip BMD: Details of Main Efficacy Results in Berlex Analyses**

Treatment	Statistics	Visit 3/Month 12		Visit 6/Month 24		12-Month Endpoint (2)		24-Month Endpoint (2)	
		Change	% Change	Change	% Change	Change	% Change	Change	% Change
E2 Ultra-low (N=209)	n	197	197	172	172	189	189	189	189
	Mean	0.007	0.914	0.007	0.883	0.007	0.804	0.007	0.837
	Median	0.006	0.855	0.010	1.091	0.006	0.839	0.006	1.035
	SD	0.0202	2.15289	0.0219	2.6902	0.0201	2.5748	0.0218	2.6489
	Minimum Maximum	-0.054 0.082	-8.290 7.710	-0.067 0.088	-9.242 9.188	-0.054 0.082	-8.290 7.710	-0.067 0.088	-9.242 9.188
Placebo (N=209)	n	180	180	180	180	184	184	185	185
	Mean	-0.002	-0.162	-0.007	-0.821	-0.002	-0.228	-0.006	-0.714
	Median	0.001	0.053	-0.008	-0.710	0.000	0.003	-0.005	-0.618
	SD	0.0228	2.6390	0.0284	3.4527	0.0231	2.8885	0.0285	3.3830
	Minimum Maximum	-0.073 0.103	-7.059 10.844	-0.119 0.091	-13.672 10.489	-0.073 0.103	-7.059 10.844	-0.119 0.091	-13.672 10.489
P-value (1)					<0.001 (a)	<0.001 (a)	<0.001 (a)	<0.001 (a)	

Table 24: Change and Percent Change From Baseline in Bone Mineral Density (g/cm<sup>2</sup>) of Total Hip by Treatment Group and Visit - Full Analysis Set

Table 26: Proportion of Subjects With No Loss (Change >= 0) in Total Hip Bone Mineral Density - Full Analysis Set

Treatment	Statistics	Visit 3/Month 12	Visit 6/Month 24	12-Month Endpoint (2)	24-Month Endpoint (2)
E2 Ultra-low (N=209)	n	197	172	189	189
	Change >= 0	124 (63%)	110 (64%)	128 (68%)	120 (63%)
	Lower Upper	80% 73%	67% 71%	55% 73%	57% 70%
Placebo (N=209)	n	180	180	184	185
	Change >= 0	91 (51%)	66 (41%)	82 (50%)	79 (43%)
	Lower Upper	43% 58%	34% 49%	43% 57%	38% 50%
	P-value (1) Odds ratio 95% C.I. for odds ratio			0.001 1.88 (1.30, 3.03)	<0.001 2.37 (1.65, 3.62)

Lower and Upper refer to the 95% lower and upper asymptotic confidence limits for a single proportion. Only subjects who had evaluations at both baseline and the specified time point are included.  
 (1) P-value, odds ratio, and confidence interval are for between-treatment group comparisons computed from a logistic regression model with terms for treatment and center.  
 (2) Represents the last observed post baseline value (at that timepoint) carried forward.

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#### Tables 6-7. Main Efficacy Results in My Analyses

**Table 6. Mean Percent Change from Baseline In Lumbar Spine and Total Hip BMD: Baseline E2 <5 pg/mL Compared to  $\geq$ 5 pg/mL**

Patients with Baseline E2 <5 pg./mL							
Lumbar Spine				Total Hip			
	Menostar N= 110	Placebo N= 110	p-value		Menostar N= 110	Placebo N=110	p-value
	n= 101	n= 97			n= 101	n= 96	
12-month Endpoint	2.52	0.47	<0.001	12-month Endpoint	1.03	- 0.64	<0.001
	n= 101	n= 97			N= 101	n= 96	
24-month Endpoint	3.50	0.29	<0.001	24-month Endpoint	1.04	- 1.09	<0.001

Patients with Baseline E2 $\geq$ 5 pg/mL							
Lumbar Spine				Total Hip			
	Menostar N= 98	Placebo N= 99	p-value		Menostar N= 98	Placebo N=99	p-value
	n= 88	n= 89			n= 101	n= 96	
12-month Endpoint	2.04	0.55	0.003	12-month Endpoint	0.76	0.24	0.163
	n= 88	n= 89			N= 101	n= 96	
24-month Endpoint	2.40	0.81	0.002	24-month Endpoint	0.61	- 0.31	0.045

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**Table 6A. Lumbar Spine BMD: Details of Main Efficacy Results in My Analyses, 2 of 2**

TABLE 17.1: Proportion of Subjects With No Loss (Change  $\geq 0$ ) in Lumbar Spine (AP View L2-L4) Bone Mineral Density - Full Analysis Set (Covariance Baseline Estimator)  $< 5$  pg/mL subgroup

Treatment	Statistics	Visit 3/Month 12	Visit 6/Month 24	12-month Endpoint (2)	24-month Endpoint (2)
E2 titration (N=99)	n	100	92	101	101
	Change $\geq 0$	79 (79%)	76 (83%)	80 (79%)	85 (84%)
	Lower	71*	75*	71*	74*
Placebo (N=110)	n	87*	90*	87*	91*
	Change $\geq 0$	94 (55%)	84 (51%)	97 (54%)	97 (98%)
	Lower	45*	41*	44*	40*
Upper	65*	62*	64*	59*	
P-value (1)		$<0.001$			
Odds ratio		3.41			
95% C.I. for odds ratio		(1.91, 6.43)			

\*Statistical results that were too low to measure were imputed to 1.4 pg/mL. The lowest detectable level possible. Lower and upper refer to the 95% lower and upper asymptotic confidence limits for a single proportion. Only subjects who had evaluations at both baseline and the specified time point are included. (1)P-value, odds ratio, and confidence interval are for between-treatment group comparisons computed from the generalized Cochran-Mantel-Haenszel test, stratified by center. The generalized CMH test was used because the logistic regression model, stratified by center, did not converge. (2)Represents the last observed post baseline value (at last timepoint) carried forward.

TABLE 17.2: Proportion of Subjects With No Loss (Change  $\geq 0$ ) in Lumbar Spine (AP View L2-L4) Bone Mineral Density - Full Analysis Set (Covariance Baseline Estimator)  $\geq 5$  pg/mL subgroup

Treatment	Statistics	Visit 3/Month 12	Visit 6/Month 24	12-month Endpoint (2)	24-month Endpoint (2)
E2 titration (N=99)	n	27	31	30	30
	Change $\geq 0$	26 (78%)	31 (74%)	27 (78%)	26 (75%)
	Lower	27*	28*	27*	26*
Placebo (N=99)	n	35*	35*	39	39
	Change $\geq 0$	48 (55%)	46 (51%)	48 (54%)	56 (83%)
	Lower	44*	50*	44*	53*
Upper	65*	72*	64*	73*	
P-value (1)		0.002			
Odds ratio		2.79			
95% C.I. for odds ratio		(1.45, 5.37)			

\*Statistical results that were too low to measure were imputed to 1.4 pg/mL. The lowest detectable level possible. Lower and upper refer to the 95% lower and upper asymptotic confidence limits for a single proportion. Only subjects who had evaluations at both baseline and the specified time point are included. (1)P-value, odds ratio, and confidence interval are for between-treatment group comparisons computed from the generalized Cochran-Mantel-Haenszel test, stratified by center. The generalized CMH test was used because the logistic regression model, stratified by center, did not converge. (2)Represents the last observed post baseline value (at last timepoint) carried forward.

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**Table 7. Percent of Patients with No Loss in Lumbar Spine and Total Hip  
BMD: Baseline E2 <5 pg/mL Compared to ≥5 pg/mL**

Patients with Baseline E2 <5 pg/mL							
Lumbar Spine				Total Hip			
	Menostar N= 110	Placebo N= 110	p-value		Menostar N= 110	Placebo N=110	p-value
	n= 101	n= 97			n= 101	n= 96	
12-month Endpoint	79%	54%	<0.001	12-month Endpoint	69%	43%	<0.001
	n= 101	n= 97			N= 101	n= 96	
24-month Endpoint	84%	49%	<0.001	24-month Endpoint	64%	38%	<0.001

Patients with Baseline E2 ≥5 pg/mL							
Lumbar Spine				Total Hip			
	Menostar N= 98	Placebo N= 99	p-value		Menostar N= 98	Placebo N=99	p-value
	n= 88	n= 89			n= 101	n= 96	
12-month Endpoint	76%	54%	0.002	12-month Endpoint	63%	58%	0.501
	n= 88	n= 89			N= 101	n= 96	
24-month Endpoint	75%	63%	0.090	24-month Endpoint	63%	48%	0.046

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**Tables 7A. Total Hip BMD: Details of Main Efficacy Results in My Analyses, 1 of 2**

Treatment	Statistics	Visit 3/Month 12		Visit 6/Month 24		12-Month Endpoint (2)		24-Month Endpoint (2)	
		Change	% Change	Change	% Change	Change	% Change	Change	% Change
E2 uterolow (N= 93)	n	100	100	92	92	101	101	101	101
	Mean	0.008	1.039	0.008	1.183	0.008	1.033	0.008	1.038
	Median	0.002	0.831	0.012	1.421	0.008	0.824	0.010	1.144
	SD	0.0199	2.4780	0.0223	2.8662	0.0189	2.4616	0.0216	2.7899
	Maximum	-0.054	-6.290	-0.057	-9.242	-0.054	-6.290	-0.057	-9.242
Placebo (N=110)	n	93	93	94	94	96	96	96	96
	Mean	-0.006	-0.589	-0.011	-1.279	-0.006	-0.644	-0.010	-1.087
	Median	-0.002	-0.211	-0.009	-0.891	-0.002	-0.295	-0.008	-0.912
	SD	0.0220	2.6054	0.0301	3.4674	0.0222	2.6885	0.0294	3.4556
	Maximum	-0.056	-7.059	-0.119	-13.872	-0.056	-7.059	-0.119	-13.672
F-value (1)		0.046	5.453	0.091	10.489	0.046	5.453	0.091	10.489
				<0.001		<0.001 (a)		<0.001 (a)	<0.001 (a)

  

Treatment	Statistics	Visit 3/Month 12		Visit 6/Month 24		12-Month Endpoint (2)		24-Month Endpoint (2)	
		Change	% Change	Change	% Change	Change	% Change	Change	% Change
E2 uterolow (N= 93)	n	97	97	90	90	98	98	98	98
	Mean	0.005	0.770	0.005	0.573	0.005	0.726	0.005	0.608
	Median	0.005	0.856	0.008	0.825	0.005	0.675	0.005	0.826
	SD	0.0216	2.5921	0.0213	2.4535	0.0215	2.5805	0.0216	2.4899
	Maximum	-0.046	-5.519	-0.049	-6.079	-0.046	-5.519	-0.049	-6.079
Placebo (N= 93)	n	97	97	76	76	88	88	88	88
	Mean	0.003	0.295	-0.001	-0.315	0.002	0.237	-0.002	-0.311
	Median	0.002	0.247	-0.001	-0.112	0.002	0.197	-0.001	-0.147
	SD	0.0230	2.6039	0.0279	3.3872	0.0234	2.8461	0.0270	3.2747
	Maximum	-0.073	-6.512	-11.719	-7.773	-0.073	-6.512	-0.085	-11.719
F-value (1)		0.103	10.644	0.103	7.773	0.103	10.644	0.075	7.773
				0.169 (a)		0.169 (a)		0.093 (a)	0.045 (a)

\*Statistical results that were too low to measure were imputed to 1.4 pg/mL, the lowest detectable level possible.  
 (1) F-values are for between-treatment group comparisons. Result ANCOVA model has terms for treatment, center, and baseline as a covariate. (a) - response rank transformed. (b) - baseline omitted. (c) - treatment by center interaction added.  
 (2) Represents the last observed post baseline value (at that endpoint) carried forward.

**TABLE 24.21 Change and Percent Change from Baseline in Bone Mineral Density (BMD) of Total Hip by Treatment Group and Visit - Full Analysis Set (Covariate Baseline Estimator)\* < 5 pg/mL subgroup)**

\*Statistical results that were too low to measure were imputed to 1.4 pg/mL, the lowest detectable level possible.  
 (1) F-values are for between-treatment group comparisons. Result ANCOVA model has terms for treatment, center, and baseline as a covariate. (a) - response rank transformed. (b) - baseline omitted. (c) - treatment by center interaction added.  
 (2) Represents the last observed post baseline value (at that endpoint) carried forward.

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**Tables 7A. Total Hip BMD: Details of Main Efficacy Results in My Analyses, 2 of 2**

TABLE 25\_1: Proportion of Subjects With No Loss (Change  $\geq 0$ ) in Total Hip Bone Mineral Density  
- Full Analysis Set (Ovarian Baseline Estimator)  $< 5$  pg/ml subgroup

Treatment	Statistics	Visit 3/Month 12	Visit 6/Month 24	12-month Endpoint (2)	24-month Endpoint (2)
Z2 Urethral (N=110)	n	100	92	101	101
	Change $\geq 0$	69 (69%)	69 (75%)	70 (69%)	82 (81%)
	Lower	60	58	60	52
Upper	78	78	78	74	
Placebo (N=110)	n	93	84	96	96
	Change $\geq 0$	40 (43%)	30 (36%)	41 (43%)	36 (38%)
	Lower	33	25	33	28
Upper	53	46	53	47	
P-value (1)				<0.001	<0.001
Odds ratio				3.05	3.05
95% C.I. for odds ratio				(1.67, 5.54)	(1.67, 5.54)

\*Standard results that were too low to measure were imputed to 1.4 pg/ml, the lowest detectable level possible. Lower and upper refer to the 95% lower and upper asymptotic confidence limits for a single proportion. Only subjects who had evaluations at both baseline and the specified time point are included. (1)P-value, odds ratio, and confidence interval are for between-treatment group comparisons computed from the generalized Cochran-Mantel-Haenszel test, stratified by center. The generalized CMH test was used because the logistic regression model, stratified by center, did not converge. (2)Represents the last observed post baseline value (at that timepoint) carried forward.

TABLE 25\_2: Proportion of Subjects With No Loss (Change  $\geq 0$ ) in Total Hip Bone Mineral Density  
- Full Analysis Set (Ovarian Baseline Estimator)  $\geq 5$  pg/ml subgroup

Treatment	Statistics	Visit 3/Month 12	Visit 6/Month 24	12-month Endpoint (2)	24-month Endpoint (2)
Z2 Urethral (N=99)	n	87	80	88	89
	Change $\geq 0$	85 (98%)	80 (100%)	85 (97%)	85 (96%)
	Lower	82	82	82	82
Upper	73	73	73	73	
Placebo (N=99)	n	87	76	88	89
	Change $\geq 0$	51 (59%)	36 (47%)	51 (58%)	43 (48%)
	Lower	48	36	48	38
Upper	59	59	68	58	
P-value (1)				0.501	0.046
Odds ratio				1.23	1.98
95% C.I. for odds ratio				(0.89, 2.23)	(1.02, 2.47)

\*Standard results that were too low to measure were imputed to 1.4 pg/ml, the lowest detectable level possible. Lower and upper refer to the 95% lower and upper asymptotic confidence limits for a single proportion. Only subjects who had evaluations at both baseline and the specified time point are included. (1)P-value, odds ratio, and confidence interval are for between-treatment group comparisons computed from the generalized Cochran-Mantel-Haenszel test, stratified by center. The generalized CMH test was used because the logistic regression model, stratified by center, did not converge. (2)Represents the last observed post baseline value (at that timepoint) carried forward.

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**Table 8. Mean Percent Change from Baseline in Lumbar Spine and Total Hip BMD for Subgroups defined by CPMP Guidance**

	Lumbar spine			Total hip		
	Ultra-low Estradiol	Placebo	p-value	Ultra-low Estradiol	Placebo	p-value
<b>Subgroup I</b>	N = 32	N = 26		N = 32	N = 26	
	n = 30	n = 22		n = 30	n = 22	
12-Month Endpoint	1.65	-0.02	NS	1.00	-0.53	NS
	n = 30	n = 22		n = 30	n = 22	
24-Month Endpoint	2.87	0.31	0.018	0.39	-1.00	NS
<b>Subgroup II</b>	N = 52	N = 35		N = 52	N = 35	
	n = 50	n = 30		n = 50	n = 30	
12-Month Endpoint	1.89	0.00	0.022	0.84	-0.26	NS
	n = 50	n = 30		n = 50	n = 30	
24-Month Endpoint	2.36	0.52	0.047	0.23	-0.90	NS
<b>Subgroup III</b>	N = 107	N = 107		N = 107	N = 107	
	n = 95	n = 90		n = 95	n = 88	
12-Month Endpoint	2.53	0.14	<0.001	1.11	-0.58	<0.001
	n = 95	n = 90		n = 95	n = 89	
24-Month Endpoint	3.19	0.43	<0.001	0.83	-1.25	<0.001

N = total number of patients in each treatment group within each subgroup; n = number of patients with data available; NS = not statistically significant.

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**Table 9. Change from Baseline in Serum Osteocalcin**

Treatment Group	Statistic	Change (ng/mL) From Baseline			
		Visit 3 Month 12	12-Month Endpoint <sup>a</sup>	Visit 6 Month 24	24-Month Endpoint <sup>a</sup>
Ultra-Low Estradiol (N = 208)	n	182	185	171	189
	Mean	-3.8	-3.8	-6.9	-6.7
	Median	-3.0	-3.1	-6.1	-5.9
	SD	6.0	6.0	5.9	6.2
	Minimum	-27.4	-27.4	-29.4	-29.4
	Maximum	17.4	17.4	9.1	9.1
Placebo (N = 209)	n	179	185	158	186
	Mean	0.7	0.7	-3.5	-3.0
	Median	-0.1	-0.2	-3.6	-3.2
	SD	6.5	6.5	6.5	6.8
	Minimum	-14.2	-14.2	-24.0	-24.0
	Maximum	27.3	27.3	21.3	21.3
	<sup>b</sup> p-value		<0.001 <sup>cd</sup>		<0.001 <sup>cd</sup>

N = total number of patients; n = number of patients with data available; SD = standard deviation.

<sup>a</sup>Represents the last observed postbaseline value (at that timepoint) carried forward.

<sup>b</sup>P-values are for between-treatment group comparisons. Default ANCOVA model has terms for treatment, center, and baseline as a covariate. (c) - response rank transformed; (d) - baseline omitted.

**Table 10. Change from Baseline in Serum Bone Specific Alkaline Phosphatase**

Treatment Group	Statistic	Change (ng/mL) From Baseline			
		Visit 3 Month 12	12-Month Endpoint <sup>a</sup>	Visit 6 Month 24	24-Month Endpoint <sup>a</sup>
Ultra-low Estradiol (N = 208)	n	180	183	171	190
	Mean	-2.9	-2.8	-2.9	-2.9
	Median	-2.5	-2.5	-2.3	-2.2
	SD	5.1	5.0	4.3	4.5
	Minimum	-25.1	-25.1	-17.8	-17.8
	Maximum	14.1	14.1	10.3	10.3
Placebo (N = 209)	n	175	181	156	185
	Mean	-0.1	-0.2	-0.4	-0.4
	Median	-0.4	-0.4	0.0	-0.1
	SD	4.6	4.7	4.9	5.1
	Minimum	-10.6	-10.6	-12.9	-12.9
	Maximum	21.6	21.6	11.8	21.6
	<sup>b</sup> p-value		<0.001 <sup>cd</sup>		<0.001 <sup>c</sup>

N = total number of patients; n = number of patients with data available; SD = standard deviation.

<sup>a</sup>Represents the last observed postbaseline value (at that timepoint) carried forward.

<sup>b</sup>P-values are for between-treatment group comparisons. Default ANCOVA model has terms for treatment, center, and baseline as a covariate. (c) - response rank transformed; (d) - baseline omitted.

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**Table 11. Change from Baseline in Serum Carboxyterminal Telopeptide of Type 1 Collagen**

Treatment Group	Statistic	Change (ng/mL) From Baseline			
		Visit 3 Month 12	12-Month Endpoint <sup>a</sup>	Visit 6 Month 24	24-Month Endpoint <sup>a</sup>
Ultra-low Estradiol (N = 208)	n	182	184	172	189
	Mean	-0.1	-0.1	0.1	0.1
	Median	-0.2	-0.2	0.1	0.0
	SD	0.8	0.8	1.1	1.1
	Minimum	-2.9	-2.9	-2.1	-2.9
	Maximum	4.5	4.5	7.5	7.5
Placebo (N = 209)	n	177	183	158	186
	Mean	0.1	0.2	0.3	0.3
	Median	0.1	0.1	0.2	0.2
	SD	1.0	1.0	0.9	0.9
	Minimum	-2.8	-2.8	-2.5	-2.5
	Maximum	6.0	6.0	4.9	4.9
	<sup>b</sup> p-value		<0.001 <sup>c</sup>		0.001 <sup>c</sup>

N = total number of patients; n = number of patients with data available; SD = standard deviation.

<sup>a</sup>Represents the last observed postbaseline value (at that timepoint) carried forward.

<sup>b</sup>P-values are for between-treatment group comparisons. Default ANCOVA model has terms for treatment, center, and baseline as a covariate; (c) - response rank transformed.

**Table 12. Change from Baseline in Urinary Deoxypyridinoline/Creatinine Ratio**

Treatment Group	Statistic	Change (nmoles Dpd/mg creatinine) From Baseline			
		Visit 3 Month 12	12-Month Endpoint <sup>a</sup>	Visit 6 Month 24	24-Month Endpoint <sup>a</sup>
Ultra-low Estradiol (N = 208)	n	183	186	164	187
	Mean	-0.002	-0.002	-0.015	-0.013
	Median	-0.003	-0.002	-0.015	-0.012
	SD	0.026	0.026	0.026	0.025
	Minimum	-0.082	-0.082	-0.105	-0.105
	Maximum	0.094	0.094	0.098	0.098
Placebo (N = 209)	n	179	185	155	185
	Mean	0.003	0.003	-0.006	-0.005
	Median	0.001	0.001	-0.005	-0.003
	SD	0.027	0.026	0.024	0.024
	Minimum	-0.135	-0.135	-0.160	-0.160
	Maximum	0.144	0.144	0.053	0.053
	<sup>b</sup> p-value		0.012 <sup>c</sup>		<0.001 <sup>c,d</sup>

Dpd = deoxypyridinoline; N = total number of patients; n = number of patients with data available; SD = standard deviation.

<sup>a</sup>Represents the last observed postbaseline value (at that timepoint) carried forward.

<sup>b</sup>P-values are for between-treatment group comparisons. Default ANCOVA model has terms for treatment, center, and baseline as a covariate; (c) - response rank transformed; (d) - baseline omitted.

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**Table 13. Extent of Exposure to Menostar and Placebo**

Statistic	Treatment		Total
	Ultra-low Estradiol	Placebo	
N	208	209	417
Mean (SD)	654 (185)	632 (195)	643 (190)
Median	727	726	727
Minimum	7	33	7
Maximum	774	766	774

N = total number of patients; SD = standard deviation.

**Table 14. Resolution of Disagreement about Endometrial Biopsies**

Patient Number	Treatment Group	Independent Reader Results		
		First	Second	Third (Referee) Final Diagnosis
001251	Placebo	Abnormal – simple hyperplasia without cytological atypia	Normal – inactive/atrophic endometrium	Normal – benign strips/glandular lining
002018	Ultra-low Estradiol	Abnormal – cancer	Normal polyp	Abnormal – polyp/adenosarcoma

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Table 15. Baseline Endometrial Biopsy Results

Variable	Menostar (N=208) n (%)	Placebo (N=209) n (%)
No biopsy	1 ( 0.5%)	0
Insufficient tissue	42 (20.2%)	53 (25.4%)
Normal	165 (79.3%)	156 (74.6%)
Proliferative endometrium	0	0
Other endometrium*	165 (79.3%)	156 (74.6%)
Polyps	0	0
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium ( n=331)and/or  
inactive/atrophic endometrium (total n=26)

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**Table 15A. Details of Baseline Endometrial Biopsy Results and Baseline Transvaginal Ultrasonogram Results**

### Details of Baseline Endometrial Biopsy Results

Variable	Ultra-low Estradiol	Placebo	Total
	N = 208	N = 209	N = 417
	n (%)	n (%)	n (%)
Biopsy			
Yes	207 (99.5)	209 (100.0)	416 (99.8)
No	1 (0.5)	0 (0)	1 (0.2)
Biopsy Results			
Tissue insufficient for diagnosis:	42 (20.2)	53 (25.4)	95 (22.8)
Normal:	165 (79.3)	156 (74.6)	321 (77.0)
Strips of benign surface and glandular lining epithelium	150 (72.1)	145 (69.4)	295 (70.7)
Inactive/atrophic endometrium	15 (7.2)	11 (5.3)	26 (6.2)
Proliferative endometrium	0 (0)	0 (0)	0 (0)
Progesterational secretor endometrium	0 (0)	0 (0)	0 (0)
Menstrual type endometrium	0 (0)	0 (0)	0 (0)
Polyps			
No	165 (79.3)	156 (74.6)	321 (77.0)
Yes	0 (0)	0 (0)	0 (0)
Abnormal:	0 (0)	0 (0)	0 (0)
Simple hyperplasia cytological atypia	0 (0)	0 (0)	0 (0)
Complex hyperplasia without cytological atypia	0 (0)	0 (0)	0 (0)
Atypical hyperplasia	0 (0)	0 (0)	0 (0)
Cancer	0 (0)	0 (0)	0 (0)
Polyps			
No	0 (0)	0 (0)	0 (0)
Yes	0 (0)	0 (0)	0 (0)

N = total number of patients; n = number of patients with data available.

### Baseline Transvaginal Ultrasonogram Results

Variable	Statistics	Ultra-low Estradiol	Placebo	Total
		N = 208	N = 209	N = 417
Thickness (mm)	n	43	56	99
	Mean	2.5	2.7	2.6
	Median	2.2	2.5	2.4
	SD	1.1	1.9	1.6
	Minimum	1.0	0.7	0.7
	Maximum	4.6	14.0	14.0

N = total number of patients; n = number of patients with data available; SD = standard deviation.

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#### Tables 16-17. 12-month and 24-month Endpoint Endometrial Biopsy Results from Berlex Analyses

Table 16. 12-month Endpoint Endometrial Biopsy Results

Variable	Menostar (N=208) n (%)	Placebo (N=209) n (%)
No biopsy	11 ( 5.3%)	25 ( 12.0%)
Insufficient tissue	30 (14.4%)	38 (18.2%)
Normal	148 (71.2%)	125 (59.8%)
Proliferative endometrium	12 ( 5.8%)	2 ( 1.0%)
Other* endometrium	135 (64.9%)	123 ( 58.9%)
Polyps	2 ( 1.0%)	2 ( 1.0%)
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=202)and/or inactive/atrophic endometrium (n=56)

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**Table 16A. Details of 12-month Endpoint Endometrial Biopsy Results**

Variable	Month 12			12-Month Endpoint <sup>a</sup>		
	Ultra-low Estradiol N = 208 n (%)	Placebo N = 209 n (%)	Total N = 417 n (%)	Ultra-low Estradiol N = 208 n (%)	Placebo N = 209 n (%)	Total N = 417 n (%)
Biopsy <sup>b</sup>						
Yes	176 (84.6)	162 (77.5)	338 (81.1)	178 (85.6)	163 (78.0)	341 (81.8)
No	11 (5.3)	20 (9.6)	31 (7.4)	11 (5.3)	25 (12.0)	36 (8.6)
Biopsy Results						
Tissue insufficient for diagnosis:	29 (13.9)	38 (18.2)	67 (16.1)	30 (14.4)	38 (18.2)	68 (16.3)
Normal:	147 (70.7)	124 (59.3)	271 (65.0)	148 (71.2)	125 (59.8)	273 (65.5)
Strips of benign surface and glandular lining epithelium	92 (44.2)	108 (51.7)	200 (48.0)	93 (44.7)	109 (52.2)	202 (48.4)
Inactive/atrophic endometrium	42 (20.2)	14 (6.7)	56 (13.4)	42 (20.2)	14 (6.7)	56 (13.4)
Proliferative endometrium	12 (5.8)	2 (1.0)	14 (3.4)	12 (5.8)	2 (1.0)	14 (3.4)
Progesterational secretor endometrium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual type endometrium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polyps						
No	145 (69.7)	122 (58.4)	267 (64.0)	146 (70.2)	123 (58.9)	269 (64.5)
Yes	2 (1.0)	2 (1.0)	4 (1.0)	2 (1.0)	2 (1.0)	4 (1.0)
Abnormal:	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Simple hyperplasia without cytological atypia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complex hyperplasia without cytological atypia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atypical hyperplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polyps						
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = total number of patients; n = number of patients with data available

<sup>a</sup>Represents the last observed postbaseline value (at that timepoint) carried forward. For performance of biopsy (Yes/No), represents the Month 12 visit or the last visit; for biopsy results, represents the last visit for which a biopsy was taken.

<sup>b</sup>Includes only those patients who completed a Month 12 or early withdrawal visit.

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**Table 17. 24-month Endpoint Endometrial Biopsy Results**

**Table 17. 24-month Endpoint Endometrial Biopsy Results**

Variable	Menostar (N=208) n (%)	Placebo (N=209) n (%)
No biopsy	20 ( 9.6%)	33 (15.8%)
Insufficient tissue	23 ( 11.1%)	31 ( 14.8%)
Normal	156 (75.0%)	136 (65.1%)
Proliferative endometrium	7 ( 3.4%)	0
Other endometrium**	148 (71.2%)	136 (65.1%)
Polyps	2 ( 1.0%)	1 (0.5%)
Abnormal**	1 ( 0.5%)	0
Abnormal, in cervix ***	1 ( 0.5%)	0

\* benign surface/glandular lining epithelium (n=138),  
 inactive/atrophic endometrium (n=144),  
 progestational secretory endometrium (n=1), and  
 menstrual type endometrium (n=1)

\*\* atypical hyperplasia

\*\*\*endocervical polyp with atypical stroma/adenosarcoma

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**Table 17A. Details of 24-month Endpoint Endometrial Biopsy Results**

Variable	Month 24			Month 24 Endpoint <sup>a</sup>		
	Ultra-low Estradiol N = 208 n (%)	Placebo N = 209 n (%)	Total N = 417 n (%)	Ultra-low Estradiol N = 208 n (%)	Placebo N = 209 n (%)	Total N = 417 n (%)
<b>Biopsy<sup>b</sup></b>						
Yes	155 (74.5)	136 (65.1)	291 (69.8)	169 (81.3)	155 (74.2)	324 (77.7)
No	18 (8.7)	25 (12.0)	43 (10.3)	20 (9.6)	33 (15.8)	53 (12.7)
<b>Biopsy Results</b>						
Tissue insufficient for diagnosis:	13 (6.3)	18 (8.6)	31 (7.4)	23 (11.1)	31 (14.8)	54 (12.9)
<b>Normal:</b>	140 (67.3)	117 (56.0)	257 (61.6)	156 (75.0)	136 (65.1)	292 (70.0)
Strips of benign surface and glandular lining epithelium	50 (24.0)	63 (30.1)	113 (27.1)	58 (27.9)	80 (38.3)	138 (33.1)
Inactive/atrophic endometrium	83 (39.9)	54 (25.8)	137 (32.9)	88 (42.3)	56 (26.8)	144 (34.5)
Proliferative endometrium	6 (2.9)	0 (0.0)	6 (1.4)	7 (3.4)	0 (0.0)	7 (1.7)
Progesterational secretor endometrium	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.5)	0 (0.0)	1 (0.2)
Menstrual type endometrium	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
<b>Polyps</b>						
No	139 (66.8)	117 (56.0)	256 (61.4)	154 (74.0)	135 (64.6)	289 (69.3)
Yes	1 (0.5)	0 (0.0)	1 (0.2)	2 (1.0)	1 (0.5)	3 (0.7)
<b>Abnormal:</b>	2 (1.0)	0 (0.0)	2 (0.5)	2 (1.0)	0 (0.0)	2 (0.5)
Simple hyperplasia without cytological atypia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complex hyperplasia without cytological atypia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atypical hyperplasia	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.5)	0 (0.0)	1 (0.2)
Cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Polyps</b>						
No	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.5)	0 (0.0)	1 (0.2)
Yes <sup>c</sup>	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.5)	0 (0.0)	1 (0.2)

N = total number of patients; n = number of patients with data available

<sup>a</sup>Represents the last observed postbaseline value (at that timepoint) carried forward. For performance of biopsy (Yes/No), represents the Month 24 visit or the last visit; for biopsy results, represents the last visit for which a biopsy was taken.

<sup>b</sup>Includes only those patients who completed a Month 12, Month 24 or early withdrawal visit.

<sup>c</sup>Polyp with atypical stroma/adenosarcoma.

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#### Tables 18-19. 12-month and 24-month Endpoint Endometrial Biopsy Results from My Analyses

**Table 18. 12-month Endpoint Endometrial Biopsy Results**

##### Patients with Baseline E2 <5 pg/mL

Variable	Menostar (N=110) n (%)	Placebo (N=110) n (%)
No biopsy	4 ( 3.6%)	14 (12.7%)
Insufficient tissue	15 (13.6%)	21 (19.1%)
Normal	83 (75.5%)	64 (58.2%)
Proliferative endometrium	9 ( 8.2%)	0
Other* endometrium	73 (66.4%)	64 (58.2%)
Polyps	1 (0.9%)	2 (1.8%)
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=113) and inactive/atrophic endometrium (n=24)

##### Patients with Baseline E2 ≥5 pg/mL

Variable	Menostar (N=99) n (%)	Placebo (N=98) n (%)
No biopsy	7 ( 7.1%)	11 (11.1%)
Insufficient tissue	15 (15.3%)	17 (17.2%)
Normal	65 (66.3%)	61 (61.6%)
Proliferative endometrium	3 ( 3.1%)	2 ( 2.0%)
Other* endometrium	62 (63.3%)	59 (59.6%)
Polyps	1 ( 1.0%)	0
Abnormal	0	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=89) and inactive/atrophic endometrium (n=32)

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**Table 19. 24-month Endpoint Endometrial Biopsy Results**

**Table 19. 24-month Endpoint Endometrial Biopsy Results**

**Patients with Baseline E2 <5 pg/mL**

Variable	Menostar (N=110) n (%)	Placebo (N=110) n (%)
No biopsy	8 ( 7.3%)	17 (15.5%)
Insufficient tissue	14 (12.7%)	13 (11.8%)
Normal	84 (76.4%)	74 (67.3%)
Proliferative endometrium	2 ( 1.8%)	0
Other endometrium*	81 (73.6%)	74 (67.3%)
Polyps	2 ( 1.8%)	1 ( 0.9%)
Abnormal**	0	0
Abnormal, in cervix	1 ( 0.9%)	

\* benign surface/glandular lining epithelium (total n=81) and inactive/atrophic endometrium (total n=74)

\*\*endocervical and polyp with atypical stroma/adenosarcoma

**Patients with Baseline E2 ≥5 pg/mL**

Variable	Menostar (N=98) n (%)	Placebo (N=99) n (%)
No biopsy	12 (12.2%)	16 (16.2%)
Insufficient tissue	9 ( 9.2%)	18 (18.2%)
Normal	72 (73.5%)	62 (62.6%)
Proliferative endometrium	5 ( 5.1%)	0
Other endometrium*	67 (68.4%)	62 (62.6%)
Polyps	0	0
Abnormal**	1 ( 1.0%)	0
Abnormal, in cervix	0	0

\* benign surface/glandular lining epithelium (n=57), inactive/atrophic endometrium (n=70), progestational/secretory endometrium (n=1), and menstrual type endometrium (n=1)

\*\*atypical hyperplasia

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**Table 20. Serious Adverse Events (SAEs)**

Body System/Preferred Term	Treatment	
	Ultra-low estradiol N = 208 n (%)	Placebo N = 209 n (%)
Number (%) of patients with a serious adverse events	24 (11.5)	23 (11.0)
<b>Body as a Whole</b>	5 (2.4)	7 (3.3)
Abdominal pain	0 (0.0)	2 (1.0)
Accidental injury	2 (1.0)	0 (0.0)
Aggravation reaction	1 (0.5)	0 (0.0)
Back pain	0 (0.0)	1 (0.5)
Hernia	0 (0.0)	2 (1.0)
Pain	0 (0.0)	1 (0.5)
Sarcoma	0 (0.0)	1 (0.5)
Surgery	2 (1.0)	2 (1.0)
<b>Cardiovascular System</b>	3 (1.4)	7 (3.3)
Angina pectoris	0 (0.0)	1 (0.5)
Arterial anomaly	1 (0.5)	0 (0.0)
Arterial thrombosis	1 (0.5)	0 (0.0)
Arterial fibrillation	0 (0.0)	1 (0.5)
Bradycardia	1 (0.5)	0 (0.0)
Cerebrovascular infarct	0 (0.0)	1 (0.5)
Cerebrovascular accident	0 (0.0)	1 (0.5)
Chest pain	0 (0.0)	1 (0.5)
Coronary artery disorder	0 (0.0)	1 (0.5)
Hypertension	1 (0.5)	0 (0.0)
Palpitation	1 (0.5)	0 (0.0)
Varicose vein	0 (0.0)	1 (0.5)
<b>Digestive System</b>	4 (1.9)	5 (2.4)
Cholelithiasis	0 (0.0)	1 (0.5)
Colitis	1 (0.5)	0 (0.0)
<b>Dyspepsia</b>	1 (0.5)	0 (0.0)
Gastrointestinal carcinoma	0 (0.0)	1 (0.5)
Gastrointestinal disorder	1 (0.5)	0 (0.0)
Intestinal obstruction	1 (0.5)	0 (0.0)
Large intestine perforation	0 (0.0)	1 (0.5)
Pancreatitis	0 (0.0)	1 (0.5)
Rectal bleeding	0 (0.0)	1 (0.5)
Rectal disorder	0 (0.0)	1 (0.5)

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Body System/Preferred Term	Treatment	
	Ultra-low estradiol N = 208 n (%)	Placebo N = 209 n (%)
Hemic and lymphatic	1 (0.5)	0 (0.0)
Iron deficiency anemia	1 (0.5)	0 (0.0)
Musculoskeletal System	6 (2.9)	2 (1.0)
Arthralgia	3 (1.4)	1 (0.5)
Arthritis	2 (1.0)	1 (0.5)
Bone fracture (not spontaneous)	1 (0.5)	0 (0.0)
Bone disorder	1 (0.5)	0 (0.0)
Nervous System	2 (1.0)	1 (0.5)
Convulsion	0 (0.0)	1 (0.5)
Headache	1 (0.5)	0 (0.0)
Hypoesthesia	1 (0.5)	0 (0.0)
Respiratory System	4 (1.9)	1 (0.5)
Carcinoma of lung	1 (0.5)	0 (0.0)
Lung disorder	2 (1.0)	0 (0.0)
Pleural effusion	1 (0.5)	0 (0.0)
Pneumonia	1 (0.5)	1 (0.5)
Skin and Appendages	2 (1.0)	2 (1.0)
Breast carcinoma	1 (0.5)	2 (1.0)
Skin carcinoma	1 (0.5)	0 (0.0)
Special Senses	1 (0.5)	0 (0.0)
Vestibular disorder	1 (0.5)	0 (0.0)
Urogenital System	3 (1.4)	3 (1.4)
Cervix carcinoma	0 (0.0)	1 (0.5)
Cervix neoplasm	1 (0.5)	0 (0.0)
Ovarian disorder	0 (0.0)	1 (0.5)
Urinary tract infection	1 (0.5)	0 (0.0)
Uterine disorder	1 (0.5)	1 (0.5)

N = total number of patients; n = number of patients with data available

This table includes all adverse events with a start date that occurred on or after study treatment date with the following exception: Adverse events with start date after the last study day are not included.

Patients with more than 1 occurrence of same adverse event were counted once.

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**Table 21. Discontinuations due to AEs**

Preferred Term	Treatment	
	Ultra-low estradiol N = 208 n (%)	Placebo N = 209 n (%)
Number (%) of patients with adverse events that caused discontinuation of study medication	21 (10.1)	21 (10.0)
Flatulence	3 (1.4)	0 (0.0)
Weight gain	2 (1.0)	0 (0.0)
Application site reaction	2 (1.0)	5 (2.4)
Nausea	2 (1.0)	0 (0.0)
Abdominal pain	1 (0.5)	0 (0.0)
Aggravation reaction	1 (0.5)	0 (0.0)
Alopecia	1 (0.5)	0 (0.0)
Amnesia	1 (0.5)	0 (0.0)
Arterial anomaly	1 (0.5)	0 (0.0)
Arterial thrombosis	1 (0.5)	0 (0.0)
Arthritis	1 (0.5)	0 (0.0)
Asthenia	1 (0.5)	1 (0.5)
Breast engorgement	1 (0.5)	0 (0.0)
Breast pain	1 (0.5)	0 (0.0)
Carcinoma of the lung	1 (0.5)	0 (0.0)
Central nervous system disorder	1 (0.5)	0 (0.0)
Chest Pain	1 (0.5)	0 (0.0)
Dyspnea	1 (0.5)	0 (0.0)
Emotional lability	1 (0.5)	0 (0.0)
Endometrial neoplasm	1 (0.5)	0 (0.0)
Headache	1 (0.5)	2 (1.0)
Hot flashes	1 (0.5)	1 (0.5)
Malaise	1 (0.5)	1 (0.5)
Nail disorder	1 (0.5)	0 (0.0)
Pain in extremity	1 (0.5)	0 (0.0)
Pelvic Pain	1 (0.5)	0 (0.0)
Sore throat	1 (0.5)	0 (0.0)
Syncope	1 (0.5)	0 (0.0)

N = total number of patients; n = number of patients with data available.

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Patients with more than 1 occurrence of same adverse event were counted once.

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**Table 22. AEs in General**

Body System	Treatment	
	Ultra-low estradiol N = 208 n (%)	Placebo N = 209 n (%)
Number (%) of patients with at least 1 adverse event	194 (93.3)	185 (88.5)
Body as a Whole	102 (49.0)	106 (50.7)
Cardiovascular System	32 (15.4)	34 (16.3)
Digestive System	63 (30.3)	60 (28.7)
Endocrine System	7 (3.4)	5 (2.4)
Hemic and Lymphatic System	8 (3.8)	7 (3.3)
Injection Reactions	0 (0.0)	1 (0.5)
Metabolic and Nutritional Disorders	33 (15.9)	30 (14.4)
Musculoskeletal System	58 (27.9)	53 (25.4)
Nervous System	53 (25.5)	38 (18.2)
Respiratory System	68 (32.7)	72 (34.4)
Skin and Appendages	62 (29.8)	65 (31.1)
Special Senses	24 (11.5)	24 (11.5)
Urogenital System	82 (39.4)	56 (26.8)

N = total number of patients; n = number of patients with data available.

This table includes all adverse events with a start date that occurred on or after study treatment date with the following exception: Adverse events with start date after the last study day are not included.

Patients with more than 1 occurrence of same adverse event were counted once.

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**Table 23. Urogenital System: Any AE**

Body System / Preferred Term	E2 Ultralow (N=208) n(%)	Placebo (N=208) n(%)
<b>Urogenital System</b>	<b>82( 39.4)</b>	<b>56( 26.8)</b>
Cervicitis	3( 1.4)	1( 0.5)
Cervix carcinoma	0( 0.0)	1( 0.5)
Cervix disorder	6( 2.9)	6( 2.9)
Cervix neoplasm	13( 6.3)	4( 1.9)
Cystitis	4( 1.9)	1( 0.5)
Dysuria	2( 1.0)	0( 0.0)
Endometrial disorder	2( 1.0)	0( 0.0)
Endometrial hyperplasia	1( 0.5)	0( 0.0)
Endometrial neoplasm	3( 1.4)	0( 0.0)
Female genital pain	1( 0.5)	0( 0.0)
Genital leukoplakia	0( 0.0)	1( 0.5)
Hematuria	2( 1.0)	2( 1.0)
Kidney calculus	1( 0.5)	0( 0.0)
Labial edema	1( 0.5)	0( 0.0)
Leukorrhea	22( 10.6)	3( 1.4)
Ovarian Cyst	1( 0.5)	1( 0.5)
Ovarian disorder	1( 0.5)	1( 0.5)
Papanicolaou smear suspicious	4( 1.9)	4( 1.9)
Proteinuria	0( 0.0)	1( 0.5)
Pyuria	0( 0.0)	1( 0.5)
Salpingitis	1( 0.5)	0( 0.0)
Urinary incontinence	2( 1.0)	1( 0.5)
Urinary tract disorder	2( 1.0)	0( 0.0)
Urinary tract infection	19( 8.7)	19( 9.1)
Urinary urgency	0( 0.0)	1( 0.5)
Urine abnormality	2( 1.0)	3( 1.4)
Urogenital disorder	1( 0.5)	1( 0.5)
Urogenital neoplasm	0( 0.0)	1( 0.5)
Uterine disorder	7( 3.4)	2( 1.0)
Uterine fibroids degenerated	0( 0.0)	1( 0.5)
Uterine hemorrhage	1( 0.5)	0( 0.0)
Uterine neoplasm	0( 0.0)	1( 0.5)
Vaginal Dryness	0( 0.0)	1( 0.5)
Vaginal hemorrhage	7( 3.4)	4( 1.9)
Vaginal nonlithiasis	3( 1.4)	0( 0.0)
Vaginitis	2( 1.0)	1( 0.5)
Vulvovaginal disorder	5( 2.4)	3( 1.4)
Vulvovaginitis	1( 0.5)	0( 0.0)

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 This table includes all adverse events with a start date that occurred on or after study treatment date with the following exception: Adverse events with start date after the last study day are not included. Subjects with more than one occurrence of same adverse event were counted once.  
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**Table 24. Nervous System: Any AE**

Body System / Preferred Term	E2 Ultracow (N=209) n(%)	Placebo (N=209) n(%)
Nervous System	53 ( 25.5)	38 ( 18.2)
Amnesia	1 ( 0.5)	1 ( 0.5)
Anxiety	5 ( 2.4)	4 ( 1.9)
Central nervous system disorder	2 ( 1.0)	0 ( 0.0)
Central nervous system neoplasm	0 ( 0.0)	1 ( 0.5)
Concentration ability impaired	0 ( 0.0)	1 ( 0.5)
Convulsion	0 ( 0.0)	1 ( 0.5)
Depression	6 ( 2.9)	3 ( 1.4)
Dizziness	11 ( 5.3)	6 ( 2.9)
Dry mouth	1 ( 0.5)	1 ( 0.5)
Emotional lability	1 ( 0.5)	0 ( 0.0)
Euphoria	0 ( 0.0)	1 ( 0.5)
Extrapyramidal syndrome	1 ( 0.5)	0 ( 0.0)
Headache	9 ( 4.3)	11 ( 5.3)
Hot Flashes	5 ( 2.4)	1 ( 0.5)
Hypertonia	1 ( 0.5)	2 ( 1.0)
Hypesthesia	3 ( 1.4)	1 ( 0.5)
Incoordination	0 ( 0.0)	1 ( 0.5)
Insomnia	3 ( 1.4)	4 ( 1.9)
Libido decreased	0 ( 0.0)	1 ( 0.5)
Multiple sclerosis	1 ( 0.5)	0 ( 0.0)
Nervousness	1 ( 0.5)	1 ( 0.5)
Neuralgia	3 ( 1.4)	2 ( 1.0)
Neuropathy	4 ( 1.9)	0 ( 0.0)
Paralysis	0 ( 0.0)	1 ( 0.5)
Paresthesia	2 ( 1.0)	2 ( 1.0)
Reflexes decreased	0 ( 0.0)	1 ( 0.5)
Sweating increased	4 ( 1.9)	1 ( 0.5)
Tremor	2 ( 1.0)	1 ( 0.5)
Vertigo	0 ( 0.0)	4 ( 1.9)

This table includes all adverse events with a start date that occurred on or after study treatment date with the following exception: Adverse events with start date after the last study day are not included. Subjects with more than one occurrence of same adverse event were counted once.

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**Table 25. Plasma Hormone Levels**

Lab Test (Normal range)	Ultra-low Estradiol			Placebo		
	Screening	12-Month	24-Month or Last Visit	Screening	12-Month	24-Month or Last Visit
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Estrone (pg/mL) <sup>a</sup>	32.5 (12.7)	31.0 (13.6)	36.8 (15.4)	32.2 (12.9)	29.4 (12.6)	34.5 (16.0)
Estradiol (pg/mL) <sup>a</sup>	6.9 (5.8)	12.7 (25.1)	11.2 (7.9)	7.8 (6.3)	6.9 (5.1)	8.2 (10.2)
SHBG (20-100 nmol/L)	45.1 (20.1)	45.9 (21.1)	46.6 (20.9)	44.5 (20.8)	43.1 (18.5)	43.9 (20.0)

SD = standard deviation; SHBG = sex hormone binding globulin.  
<sup>a</sup>No normal range available

**Table 26. Maturation Index**

Treatment	Visit	Pattern Type				Total n(%)	P-Value (2)
		Mature n(%)	Indeterminate n(%)	Immature n(%)	Not Done (1) n(%)		
E2 Ultralow (N=209)	Screening Visit	0 ( 0 )	3 (33.3)	5 (55.6)	1 (11.1)	9 ( 100)	
	Visit 3/Month 12	0 ( 0 )	126 (67.0)	25 (13.3)	37 (19.7)	188 ( 100)	
	Visit 6/Month 24	1 ( 0.5)	110 (63.6)	25 (14.5)	37 (21.4)	173 ( 100)	
	*Final Visit	1 ( 0.5)	134 (71.3)	33 (17.6)	20 (10.6)	188 ( 100)	
Placebo (N=209)	Screening Visit	0 ( 0 )	2 (33.3)	3 (50.0)	1 (16.7)	6 ( 100)	
	Visit 3/Month 12	0 ( 0 )	52 (28.4)	91 (49.7)	40 (21.9)	183 ( 100)	
	Visit 6/Month 24	0 ( 0 )	33 (20.6)	70 (43.8)	57 (35.6)	160 ( 100)	
	*Final Visit	0 ( 0 )	56 (30.6)	106 (67.9)	21 (11.5)	183 ( 100)	<0.001

Data for Maturation Index was not recorded on most participants at screening.  
<sup>a</sup>Represents the month 24 visit or the last visit.

(1) The category Not Done is unsatisfactory specimens.

(2) P-value for between-treatment group comparison was only determined for Final Visit and was obtained from generalized Cochran-Mantel-Haenszel test, stratified by center.

**Table 27. Maturation Value**

Treatment	Visit	Estrogenicity Level				Total n(%)	P-Value (2)
		Low n(%)	Moderate n(%)	High n(%)	Not Done (1) n(%)		
E2 Ultralow (N=209)	Screening Visit	7 (77.8)	1 (11.1)	0 ( 0 )	1 (11.1)	9 ( 100)	
	Visit 3/Month 12	45 (23.9)	104 (65.3)	3 ( 1.6)	36 (19.1)	188 ( 100)	
	Visit 6/Month 24	35 (20.2)	91 (62.8)	10 ( 5.8)	37 (21.4)	173 ( 100)	
	*Final Visit	50 (26.6)	108 (67.4)	10 ( 5.3)	20 (10.6)	188 ( 100)	
Placebo (N=209)	Screening Visit	4 (66.7)	1 (16.7)	0 ( 0 )	1 (16.7)	6 ( 100)	
	Visit 3/Month 12	99 (54.1)	44 (24.0)	0 ( 0 )	40 (21.9)	183 ( 100)	
	Visit 6/Month 24	72 (45.0)	27 (16.8)	1 ( 0.6)	60 (37.6)	160 ( 100)	
	*Final Visit	116 (63.4)	45 (24.6)	1 ( 0.5)	21 (11.5)	183 ( 100)	<0.001

Data for Maturation Value was not recorded on most participants at screening.

<sup>a</sup>Represents the month 24 visit or the last visit.

(1) The category Not Done is unsatisfactory specimens.

(2) P-value for between-treatment group comparison was only determined for Final Visit and was obtained from generalized Cochran-Mantel-Haenszel test, stratified by center.

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**Table 28. Musculoskeletal System AEs**

Body System / Preferred Term	E2 Ultralow (N=208) n(%)	Placebo (N=209) n(%)
<b>Musculoskeletal System</b>	58( 27.9)	53( 25.4)
Arthralgia	24( 11.5)	13( 6.2)
Arthritis	11( 5.3)	15( 7.2)
Bone Fracture (Not Spontaneous)	4( 1.9)	7( 3.3)
Bone disorder	4( 1.9)	5( 2.4)
<b>Musculoskeletal System (cont)</b>		
Bone neoplasm	0( 0.0)	1( 0.5)
Bone pain	2( 1.0)	1( 0.5)
Bursitis	3( 1.4)	2( 1.0)
Joint disorder	5( 2.4)	9( 4.3)
Myalgia	10( 4.8)	8( 2.8)
Myopathy	1( 0.5)	0( 0.0)
Osteoporosis	4( 1.9)	10( 4.8)
Tendon disorder	5( 2.4)	5( 2.4)
Tenosynovitis	3( 1.4)	3( 1.4)
Twitching	1( 0.5)	0( 0.0)

### Appendix 1. Menostar Regulatory History

Date	Regulatory Event
27 Oct 1992	IND 40,928 (Climara® estradiol transdermal system) submitted to FDA
14 Dec 1999	First draft of Protocol 98188 (Phase 3 osteoporosis prevention study) submitted to FDA for review and comment (IND 40,928; Serial No. 057)
25 Feb 2000	FDA Division of Reproductive and Urologic Drug Products (DRUDP) provided written comments on first draft of Protocol 98188
20 Mar 2000	Berlex written response (IND 40,928; Serial No. 059) to the 25 Feb 2000 DRUDP comments on first draft of Protocol 98188
17 Jul 2000	DRUDP written reply to the 20 Mar 2000 Berlex response concerning the first draft of Protocol 98188
13 Sep 2001	DRUDP informed Berlex (via phone contact) that DRUDP would remain the reviewing Division despite plans for the Division of Metabolic and Endocrine Drug Products (DMEDP) to take over osteoporosis
19 Apr 2002	Protocol 305851 (phase 1 bioavailability study) submitted to FDA for review and comment (IND 40,928; Serial No. 075)
14 Sep 2001 to 02 Apr 2002	FDA-Berlex interactions relevant to statistical analysis (Amendment 4) of Protocol 98188 (via written comment, teleconference, and phone contact)
22 Jan 2003	Pre-NDA meeting request submitted to DRUDP under NDA 20-375
10 Feb 2003	DMEDP informed Berlex (via phone contact) that DMEDP (not DRUDP) would now be the reviewing Division
20 Feb 2002	Administrative preliminary investigational new drug application (PIND) No. 66,714 assigned by DMEDP (to be used instead of NDA No. 20-375, which can't be referenced in a second division)
27 Mar 2003	Pre-NDA meeting package submitted to DMEDP (IND 66,714; Serial No. 001)
10 Apr 2003	Pre-NDA meeting with DMEDP
02 Jul 2003	New NDA No. 21-674 assigned by DMEDP

# CLINICAL REVIEW

Clinical Review Section

## Appendix 2. Climara Prescribing Information



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/s/

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Bruce Stadel  
5/13/04 02:09:00 PM  
MEDICAL OFFICER

Eric Colman  
5/13/04 02:45:07 PM  
MEDICAL OFFICER  
Agree with Dr. Stadel's assessments

## **ERRATA & ADDENDUM TO REVIEW**

NDA # 21-674

Menostar™ (estradiol, transdermal, 0.014 mg per day)

Berlex Laboratories, Inc.

Indication: Postmenopausal Osteoporosis

Reviewer: Bruce V. Stadel, MD, MPH

Dates Covered by Errata & Addendum: 9 May 2004 to 8 June 2004

Date Errata & Addendum Completed: 15 June 2004

### Errata

The following errors in the Original Review, dated 13 May 2004, and completed on 9 May 2004 are hereby corrected:

Cover page, line 13 says "...only 1 woman had proliferation at both endpoints."  
This should say "...only 2 women..."

Page 8, line 8 says "...only 1 woman had proliferation at both endpoints."  
This should say "...only 2 women..."

Page 42, lines 10-11 says "For the Menostar group minus the placebo group, the mean percentages were..." This should say "For the placebo group minus the Menostar group, the percentages were..."

### Addendum

Submissions to NDA # 21-674 that I reviewed between completion of my Original Review on 9 May 2004 and the Approval Letter on 8 June 2004 included:

Submitted to NDA on 7 June 2004

19 May 2004 fax to Dr. Stadel with information about patients with proliferative endometrium.

Submitted to NDA on 14 June 2004

1 June 2004 e-mail to Dr. Stadel with proposed wording and justification for Dosage and Administration section of Prescribing Information, and fax to Dr. Stadel with related references.

2 June 2004 e-mail to Dr. Stadel with table on vaginal bleeding and supportive summary.

3. June 2004 e-mail to Dr. Stadel with refined wording for Dosage and Administration section or Prescribing Information, a with supportive appendix, and related references.

Discussion of the above submissions between Berlex and the Division, and consideration of class labeling, led to the approved labeling regarding the Indication, the use of progestin, and endometrial biopsies.

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/s/

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Bruce Stadel  
6/15/04 03:53:51 PM  
MEDICAL OFFICER

Eric Colman  
6/15/04 04:30:20 PM  
MEDICAL OFFICER

NDA SAFETY CONSULTATION

NDA 21-674

To: Bruce Stadel, M.D.  
Medical Officer, HFD-510  
Division of Metabolism and Endocrine Drug  
Products (DMEDP)

Through: Daniel Shames, M.D.  
Division Director, HFD-510  
Division of Reproductive and Urologic Drug  
Products (DRUDP)

From: Phill H. Price, M.D.  
Medical Officer, HFD-580  
Division of Reproductive and Urologic Drug  
Products (DRUDP)

Date of Consultation: September 29, 2003

Drug Name:

Trade: Menostar  
Generic name: Estradiol Transdermal System  
Chemistry: Estradiol, USP (estra-1.3.5,-(10)-triene-3, 17 $\beta$   
diol

Sponsor: Berlex  
340 Changebridge Road  
P.O. Box 1000  
Montville, NJ 07045-1000

Pharmacologic category: Estrogen

Dosage Form: Transdermal patch

Strength: One 3.25 cm<sup>2</sup> patch contains 1.0mg estradiol  
applied weekly. The estradiol delivery rate is  
0.014mg per day.

Proposed Indication: Prevention of Osteoporosis in Postmenopausal  
Women

Related Submission: August 2, 2003

Related Documents: IND 40, 928 (Climara®), Protocol 98188 (Phase 3  
Osteoporosis prevention study), Administrative  
(PIND) No. 66714

Date NDA Submitted:

August 7, 2003

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## EXECUTIVE SUMMARY

The sponsor conducted a Phase 3 multicenter, double-blind, randomized, placebo-controlled study of 2 years duration. The primary efficacy objective was to demonstrate the effectiveness of using low dose transdermal estradiol compared to placebo in the prevention of osteoporosis in postmenopausal women with an intact uterus. The primary safety objective was to demonstrate the endometrial safety of an unopposed estradiol patch compared with placebo in postmenopausal women.

Endometrial biopsy results demonstrated a proliferative endometrium in 12 (5.8%) low-dose estradiol patients and 2 (1%) placebo patients after the 12-month visit; 7 (3.4%) low estradiol patients and zero (0%) placebo patients demonstrated proliferative endometrium after 24-months (or final) visit. After 12-months of treatment, no hyperplasia was diagnosed in either treatment group; at 24-months of treatment, there was 1 (0.5%) case of atypical endometrial hyperplasia (the precursor to endometrial cancer) in a low dose estradiol patient.

An endometrial proliferative rate of 5.8% at one year of use and 3.4% at 2 years is *too high* for unopposed estrogen use. This statement is made in the context of at baseline there were no cases of proliferation in any of the biopsy specimens. In addition, 1 case of atypical endometrial hyperplasia supports the time-tested concept that proliferation of the endometrium in any postmenopausal women needs investigation and biopsy. Therefore, if this product is approved for prevention of osteoporosis, endometrial biopsy should be standard of care for follow up; if biopsy can not be performed, an ultrasound with an endometrial stripe of 3mm is more reassuring. Endometrial stripes of equal to or greater than 4mm (if a biopsy cannot be accomplished) may require treatment with a progestin.

### 1.0 Background and Regulatory History

Endometrial carcinoma is the most common malignancy of the female genital tract, accounting for all most half of all gynecologic cancers in the United States. About 39,300 new cases are diagnosed annually, resulting in more than 6,600 deaths. Overall, about 2% to 3% of women develop endometrial cancer during their lifetime.

Endometrial cancer is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The role of estrogen in the development of most endometrial cancers has clearly been established; any factor that increases exposure to an unopposed estrogen increased the risk of for endometrial cancer.

Estrogen therapy is an established risk factor for endometrial hyperplasia and cancer. The risk for endometrial cancer is 4 to 8 times greater in postmenopausal women receiving unopposed estrogen, and the risk increased with time and higher estrogen doses. This risk can be decreased by the addition of a progestin to the estrogen, either cyclically or continuously.

Postmenopausal uterine bleeding is caused by a number of conditions. In approximately 60-80% of cases the cause of uterine bleeding is atrophic endometrium; estrogen

replacement therapy is the cause of uterine bleeding in 15-25% of cases; endometrial hyperplasia is the cause of uterine bleeding in 5-10% of cases; and endometrial cancer is the cause of uterine bleeding in 10% of cases.

Climara® (NDA 20-375) was approved on December 22, 1994. The dosages of this approved product were 0.05 and 0.1mg/day. The application was approved for once weekly application to the abdomen. Subsequent supplements to the NDA provided for additional sites other than the abdomen via pharmacokinetic studies. On March 23, 1998, the 0.075mg/day estradiol dosage was approved for the treatment of moderate to severe vasomotor symptoms; on March 5, 1999 (supplement 011) the 0.025 mg/day dose was approved for the prevention of postmenopausal osteoporosis. Supplement 011 did not provide for a vasomotor indication.

On June 2, 2000 the sponsor submitted supplement 016 which provided for the 0.025mg/day to be studied for vasomotor symptoms. The sponsor submitted two studies, one placebo controlled study and one comparative study to support Climara® (0.025mg/day) in the treatment of moderate to severe vasomotor symptoms. Supplement 016 was approved on April 5, 2001.

On December 14, 1999 the first draft of Protocol 98188 (Phase 3) osteoporosis prevention study) was submitted DRUDP for review and comment.

On February 25, 2000 DRUDP provided written comments on the first draft of Protocol 98188.

On September 13, 2001 DRUDP informed Berlex that DRUDP would remain the reviewing Division despite plans for DMEDP to take over the osteoporosis indication.

On February 10, 2003 DMEDP informed Berlex that DMEDP (not DRUDP) would now be the reviewing division.

On April 10, 2003 a Pre-NDA meeting was held with DMEDP.

On July 2, 2003 a new NDA number 21-674 was assigned by DMEDP to distinguish Menostar™ from Climara®.

## 2.0 The Approach to Evaluation of Drugs for the Treatment of Menopausal Symptoms and Osteoporosis

In August 1992 a labeling Guidance for Estrogen Drug Products was published for comment. After an Advisory Committee meeting in November 1992, pharmaceutical companies began working on estrogen/progestin products for the treatment of vasomotor symptoms (VMS) and osteoporosis. Products could either be a continuous combined method or a continuous sequential method used to protect the endometrium from unopposed estrogen. In March 1995 a Labeling Guidance was published for combination estrogen/progestin drug products which outlined how the excess risk of endometrial cancer associated with ERT and its use in the treatment of osteoporosis should be studied. Requirements for symptomatic indications (vasomotor symptoms), endometrial protection, and osteoporosis were outlined in this document and have been followed by the two primary reviewing Divisions of FDA, HFD-510 and HFD-580 since

March 1995. On September 27, 1999 a Draft Labeling Guidance (Docket 98D0834) was placed in the Federal Register and was entitled "Labeling Guidance for Noncontraceptive Estrogen Drug Products- Prescribing Information for Healthcare Providers and Patient Labeling." The previous Guidance documents was updated in January 2003 and is entitled "Labeling Guidance for Industry---Estrogen and Estrogen/Progestin Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommendations for Clinical Evaluation. Since the creation of DRUDP from the parent division, DMEDP in June 1996, there has been an overlap of indications, especially relating to osteoporosis, and a subsequent need for consultation between DMEDP and DRUDP.

### 3.0 Review of Safety Data Specifically regarding the Endometrium

**Note: This review is confined to endometrial safety data. All efficacy data and pertinent safety data other than the endometrium will be incorporated into the review done by the primary reviewer.**

The sponsor submitted a Phase 3 multicenter, double blind, randomized, placebo-controlled study to evaluate the safety and efficacy of a low dose estradiol given by continuous transdermal administration in the prevention of osteoporosis in postmenopausal women. The study was conducted at 9 sites in the US and was initiated on January 10, 2000 and completed on November 23, 2002. Approximately 410 patients with an intact uterus were planned for entrance into this study. Approximately 417 patients were analyzed in the safety data set.

The primary efficacy objective was to demonstrate the effectiveness of a low dose unopposed estradiol administered transdermally, compared with placebo for the prevention of osteoporosis in postmenopausal women. The primary safety objective was to demonstrate the endometrial safety of an unopposed estradiol patch compared with placebo in postmenopausal women with an intact uterus.

All subjects received one 3.25 cm<sup>2</sup> patch with an estradiol delivery rate of 0.014mg/day. In addition, patients received Tums® tablet (400 mg of calcium each) and Centrum® tablet (162 mg of calcium each); patients were also provided with vitamin D supplements (400IU).

#### Inclusion Criteria

Women who satisfied the following criteria were included into the study:

- Age  $\geq$  60 years and  $\leq$  80 years
- Amenorrhea for  $\geq$  5 years
- Evaluable BMD for spine and hip
- Intact uterus, ability to have endometrial biopsy performed and diagnostically valid negative endometrial biopsy. If adequate tissue, endometrial thickness < 4 mm on vaginal ultrasound, and
- Signed informed consent.

## Exclusion Criteria

Only exclusion criteria related to the endometrium are identified:

- Baseline endometrial biopsy showing simple hyperplasia or worse
- Any history of breast or endometrial cancer, or malignant melanoma
- Estrogen or progestin therapy (oral, transdermal, intramuscular, intrauterine or intravaginal administration) within 3 months prior to start of study.

**Comment: Above inclusion and exclusion criteria are consistent with previous studies for osteoporosis and vasomotor symptom studies and identify appropriate criteria that were included/excluded in previous studies.**

## Conduct of Study Relating to Endometrial Biopsy and Transvaginal Ultrasonography

Patients had endometrial biopsies performed at baseline, Visit 3 (month 12), Visit 6 (month 24), and any time when medically indicated. At baseline, Visit 3, and Visit 6, an endometrial aspiration biopsy was performed, and if needed, transvaginal ultrasonography was performed by the principal investigator and/or associate using procedures consistent with the current clinical practices at each site. *At screening, if it was not possible to enter the uterine cavity for endometrial biopsy, the participant was not enrolled.* The endometrial sample was sufficient if it contained strips of endometrial epithelium. If tissue obtained at endometrial biopsy was *insufficient* for diagnosis, vaginal ultrasound was performed and endometrial thickness of less than 4mm was considered to represent atrophic/inactive endometrium and the patient was eligible to enter the study. Women with an endometrial thickness of  $\geq 4$ mm at baseline were excluded unless a repeat endometrial biopsy was histologically normal.

A central reading laboratory was used for processing and evaluation of the endometrial biopsy slides. All endometrial biopsies were evaluated by 2 independent pathologists, located at different pathology laboratories, blinded to treatment assignment and to each other's diagnostic reading. If there were discrepancies between the first and second read, a third independent, referee pathologist evaluated the samples in order to settle the dispute and to provide a final diagnosis. This procedure was followed for disputes involving both normal and abnormal diagnoses.

**Comment: The reading of endometrial slides in this study differs from those published in the Labeling Guidance of January 2003. In the Guidance document a single pathologist reader initially assesses the slide from the endometrial biopsies obtained at screening. For the efficacy evaluation, the concurrence of two of the three pathologists is accepted for final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium) would be used as the final diagnosis. From this reviewer's perspective, the slide reading pr**

These evaluations determined eligibility for the study, discontinuation from the study and follow-up of study patients. In any patient who developed an abnormal endometrial polyp alone (no adjacent endometrial tissue analyzable) or hyperplasia or any condition more severe at any time during the study, study medication was immediately discontinued and

the patient was given appropriate treatment and follow-up. The patient was followed until resolution of endometrial pathology or until a stable clinical state was reached. Also, in cases of prolonged moderate to severe vaginal bleeding (longer than 7 days), transvaginal ultrasonography (TVS) and/or endometrial biopsy were performed indicated.

Normal tissue was defined in the following categories: Strips of benign surface and glandular lining epithelium, inactive/atrophic endometrium, proliferative endometrium, progesterational secretory endometrium, and menstrual type endometrium. Abnormal biopsy results were classified as simple hyperplasia (atypia), complex hyperplasia without atypia, atypical hyperplasia, and cancer. There was a separate designation for polyps, they were either present or not.

## RESULTS

All except 1 of 417 patients enrolled in the study had an endometrial biopsy performed at baseline. One patient did not have an endometrial biopsy at baseline due to a stenotic cervix. A total of 95 (22.8%) patients underwent transvaginal ultrasound (TVS) at baseline.

At baseline results indicate 321 (77%) of 417 patients enrolled who had sufficient tissue for diagnosis had normal tissue. Approximately 95 (22.8%) had tissue that was considered insufficient for diagnosis. In this group, 42 (20.2%) were in the low estradiol group and 53 (25.4%) was in the placebo group. There were no abnormal baseline endometrial biopsy results and no polyps were present in either group. In the group classified as normal 26 (6.2%) patients had an endometrium classified as inactive/atrophic group; of this total 15 (7.2%) were in the low dose estradiol group and 11 (5.3%) were in the placebo group. No patient in either group had endometrial tissue classified as proliferative. There did not appear to be any difference between treatment groups in the distribution of classifications of normal tissue.

At baseline the endometrial thickness was 2.5mm for the low dose estradiol group and 2.7mm for placebo patients. A placebo patient (#600013) had an endometrial thickness equal to 14mm at baseline. There was insufficient tissue for diagnosis obtained from baseline endometrial biopsy. This patient was randomized and received study medication for approximately 5 weeks. She was discontinued from the study due to protocol violation. In addition, this patient underwent a D&C for removal of an endometrial polyp; she was followed in the study until completion.

**Safety Data Summation tables**  
**12-month endometrial biopsy and TVS results**  
 Table 1

12-Month Endometrial Biopsy Results—Safety Set

Sponsor's Table 39 (unmodified)

Variable	Month 12			12- Month Endpoint		
	Ultra-Low Estradiol N=208 n(%)	Placebo N=209 n(%)	Total N=417 n(%)	Ultra-Low Estradiol N=208 n(%)	Placebo N=209 n(%)	Total N=417 n(%)
<b>Biopsy<sup>b</sup></b>						
Yes	176(84.6)	162(77.5)	338(81.1)	178(85.6)	163(78.0)	341(81.8)
No	11(5.3)	20(9.6)	31(7.4)	11(5.3)	25(12.0)	36(8.6)
<b>Biopsy results</b>						
Tissue Insufficient for Diagnosis	29(13.9)	38(18.2)	67(16.1)	30(14.4)	38(18.2)	68(16.3)
Normal	147(70.7)	124(59.3)	271(65.0)	148(71.2)	125(59.8)	273(65.5)
Strips of benign surface/glandular lining epithelium	92(44.2)	108(51.7)	200(48.0)	93(44.7)	109(52.2)	202(48.4)
Inactive/Atrophic endometrium	42(20.2)	14(6.7)	56(13.4)	42(20.2)	14(6.7)	56(13.4)
Proliferative endometrium	12(5.8)	2(1.0)	14(3.4)	12(5.8)	2(1.0)	14(3.4)
Progestational secretory endometrium	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Menstrual type endometrium	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
<b>Polyps</b>						
No	145(69.7)	122(58.4)	267(64.0)	146(70.2)	123(58.9)	269(64.5)
Yes	2(1.0)	2(1.0)	4(1.0)	2(1.0)	2(1.0)	4(1.0)
Abnormal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Simple hyperplasia with atypia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Complex hyperplasia without atypia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Atypical hyperplasia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cancer	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
<b>Polyps</b>						
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

N= total number of patients; n=number of patients with data available

<sup>a</sup>Represents the last observed post baseline value (at that time point) carried forward. For performance of biopsy (Yes/No) represents the Month 12 visit or the last visit; for biopsy results, represents the last visit which a biopsy was taken

<sup>b</sup>Includes only those patients who completed a Month 12 or early withdrawal visit

Note at month 12, 341(81.8%) of patients had an endometrial biopsy result that was the last observation carried forward (LOCF). Also note that 8.6% of patients have no biopsy; of this total 11(5.3%) were in the low dose estradiol group and 25(12.0%) were in the placebo group. In patients who had endometrial insufficient tissue for diagnosis 30 (14.4%) were in the low dose estradiol group and 38(18.2%) were in the placebo group.

Twenty-three (23) diagnoses were discrepant between the 2 primary readers. Most (21 of 23) of the disputed diagnoses involved normal results, however, 2 involved abnormal results.

Table 2  
Results of Discrepant Diagnoses for Normal/Abnormal Issues

Patient Number	Treatment Group	Independent Reader Results		
		First	Second	Third (Referee) Final Diagnosis
001251	Placebo	Abnormal-simple hyperplasia without cytological atypia	Normal-inactive/atrophic endometrium	Normal-benign strips/glandular lining
002018	Ultra-low estradiol	Abnormal-cancer	Normal polyp	Abnormal-polyp/adenosarcoma

Overall, 258/341 (73.3%) of biopsied patients had either strips of benign surface or glandular endometrium or inactive atrophic endometrium. A significant finding in postmenopausal women is proliferative endometrium. In the low dose estradiol group note 12 (5.8%) had a diagnosis of proliferative endometrium compared to 2 (1.0%) in the placebo group. Although 5.8% vs. 1% is not statistically significant, it is worrisome because proliferative endometrium is not a normal finding in the postmenopausal women and clinical investigation should be initiated. Note two benign polyps in both groups.

**Comment:** The reason that greater than twice as many placebo patients than low dose estradiol patients (21.0% vs. 5.3%) did not undergo biopsy is unclear. However, having almost 82% of patients submit to a biopsy at 12-months implies a good study with good follow-up.

Table 3  
**Safety Data Summation Tables**  
**24-month endometrial biopsy and TVS results**

Sponsor's Table 40 (unmodified)

Variable MonthEndpoint <sup>a</sup>	Month 24			24-		
	Ultra-Low	Placebo	Total	Ultra-Low	Placebo	
Total						
	Estradiol	Estradiol		Estradiol		
N=417	N=208	N=209	N=417	N=208	N=209	
n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	
<b>Biopsy<sup>b</sup></b>						
Yes	155(74.5)	136(65.1)	291(69.8)	169(81.3)	155(74.2)	324(77.7)
No	18(8.7)	25(12.0)	43(10.3)	20(9.6)	33(15.8)	53(12.7)
<b>Biopsy results</b>						
Tissue Insufficient for Diagnosis	13(6.3)	18(8.6)	31(7.4)	23(11.1)	31(14.8)	54(12.9)
Normal	140(67.3)	117(56.0)	257(61.6)	156(75.0)	136(65.1)	292(70.0)
Strips of benign surface/glandular lining epithelium	50(24.0)	63(30.1)	113(27.1)	58(27.9)	80(38.3)	138(33.1)
Inactive/Atrophic endometrium	83(39.9)	54(25.8)	137(32.9)	88(42.3)	56(26.8)	144(34.5)
Proliferative endometrium	6(2.9)	0(0.0)	6(1.4)	7(3.4)	0(0.0)	7(3.7)
Progestational secretory endometrium	1(0.5)	0(0)	1(0.2)	1(0.5)	0(0)	1(0.2)
Menstrual type endometrium	0(0)	0(0)	0(0)	1(0.5)	0(0)	1(0.2)
<b>Polyps</b>						
No	139(68.8)	117(6.0)	256(61.4)	154(74.0)	135(64.6)	289(69.3)
Yes	1(0.5)	0(0.0)	1(0.2)	2(1.0)	1(0.5)	3(0.7)
Abnormal	2(2.0)	0(0.0)	2(0.5)	2(1.0)	0(0.0)	2(0.5)
Simple hyperplasia with atypia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Complex hyperplasia without atypia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
<b>Atypical hyperplasia</b>	1(0.5)	0(0.0)	1(0.2)	1(0.5)	0(0.0)	1(0.2)
Cancer	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
<b>Polyps</b>						
No	1(0.5)	0(0.0)	1(0.2)	1(0.5)	0(0.0)	1(0.2)
Yes <sup>c</sup>	1(0.5)	0(0.0)	1(0.2)	1(0.0)	0(0.0)	1(0.2)

N= total number of patients; n=number of patients with data available

<sup>a</sup>Represents the last observed post baseline value (at that time point) carried forward. For performance of biopsy (Yes/No) represents the Month 12 visit or the last visit; for biopsy results, represents the last visit which a biopsy was taken

<sup>b</sup>Includes only those patients who completed a Month 12 or early withdrawal visit

<sup>c</sup>Polyp with atypical stroma/adenosarcoma

Note at month 24, 324(77.7%) of patients had an endometrial biopsy result that was the last observation carried forward (LOCF). Also note that 53 (12.7%) of patients have no biopsy; of this total 20 (9.6%) were in the low dose estradiol group and 33(15.8%) were in the placebo group. In patients who had endometrial tissue insufficient for diagnosis, 23 (11.1%) were in the low dose estradiol group and 31(14.8%) were in the placebo group. Overall, 287/324 (87.0%) of biopsied patients had either strips of benign surface or glandular endometrium or inactive atrophic endometrium. Significantly, as compared to the 12-month study, there was 1 case of atypical hyperplasia. This lesion is a definite precursor to endometrial carcinoma and illustrates that in some individuals that may be predisposed, unopposed estrogen, even in low dosages, may place the patient at risk for endometrial carcinoma. In the low dose estradiol group 7(3.4%) had a diagnosis of proliferative endometrium compared to 0 (0.0%) in the placebo group. Although 3.4% vs. 0% is not statistically significant, proliferative endometrium is not a normal finding in the postmenopausal women and clinical investigation is warranted. Note two polyps, in low dose estradiol group (one malignant) and in the placebo group one (benign polyp). Significantly, this malignant polyp was a stroma/adenosarcoma. This malignant tumor is not associated with estrogen therapy and probably arose de novo.

Gynecologists who follow postmenopausal women are keenly aware that any postmenopausal bleeding needs to be investigated. This is because bleeding appears to be a precursor to most cases of endometrial hyperplasia and carcinoma. The bleeding may be classified as bleeding, spotting, or both. In this study all patients who participated in the intent-to-treat (ITT) population were required to have an endometrial biopsy at baseline, at 12-month and at 24-months. In addition a significant number of patients had a transvaginal ultrasound (TVS). Study protocol required that all bleeding that occurred in excess of 7 days was to be investigated with endometrial biopsy, and if unable to obtain biopsy, a TVS. Therefore, as a secondary safety parameter, this reviewer will review bleeding. Prior to addressing bleeding it should be noted that one patient out of 50 was excluded from the analyses due to protocol violation of an endometrial stripe >4mm and a non-successful endometrial biopsy.

All bleeding in study 98188 was recorded on the basis of patient diary. In cases of prolonged bleeding (longer than 7 days) TVS and/or endometrial biopsy was performed as indicated and evaluated for safety. It is noted that patients who bled within 7 days of an endometrial biopsy are not included in this data.

The number of patients *who had bleeding* during treatment was 46 (22.1%) in the low dose estradiol group and 32 (15.3%) in the placebo group. In the low dose estradiol group, 30 of 46 patients with bleeding had a normal biopsy at 12 and 24 months and/or when an unscheduled biopsy was performed. One patient (#002018) had an abnormal biopsy result (polyp/adenosarcoma) diagnosed at 24-months of treatment. Of the remaining 15 patients tissue was insufficient for diagnosis, or the uterus could not be entered with the Pipelle® (biopsy instrument). Two patients (#100003 and #700018) did not have an endometrial thickness evaluated by TVS. Patient 100003 refused TVS and patient \_\_\_\_\_ had a hysterectomy after 12 months of treatment. Endometrial thickness

was >4mm in 4 patients via TVS. In these 4 patients, 2 had a normal or inactive/atrophic endometrium via biopsy. In the remaining 2 patients, 1 patient (9002152) had an unsuccessful endometrial biopsy with an endometrial stripe of 4.6mm, no additional test were done at 24 months; the other patient (#002204) had an endometrial thickness of 4.4mm. This patient underwent a second TVS four months later; at 24-months her endometrial biopsy was read as inactive/atrophic endometrium.

In the placebo group, 9 of 32 patients who had bleeding had a normal biopsy at 12 and 24 months and/or when an unscheduled biopsy was performed. In the remaining 23 patients, the tissue was insufficient for diagnosis or the uterus could not be entered. In addition, 5 patients had an endometrial thickness >4mm. Of these 5 patients, 4 had an endometrial biopsy that confirmed normal or inactive/atrophic endometrium. The fifth patient (#400038) had an endometrial thickness of 4.9mm at 12 months. An attempt to biopsy her was unsuccessful and further treatment was not outlined.

One patient (#400092) in the low dose estradiol group appears to have had an inadequate work-up. This patient had a baseline biopsy that revealed tissue insufficient for diagnosis. At 12-months, a TVS revealed an endometrial thickness of 4.5mm. It is noted that the *uterus was not entered* with the Pipelle® and yet the description of the biopsy revealed strips of benign surface and glandular lining epithelium that is probably from the cervix. At 24-months, a TVS revealed an endometrial stripe of 8.3mm. The uterus was not entered with the Pipelle® and the biopsy again revealed strips of benign surface and glandular lining epithelium. Clearly, if the physician states that he/she has not entered the endometrial cavity upon attempted biopsy, then additional diagnostic measures should have been performed since the endometrial stripe had increased from 4.5mm to 8.3mm. Increasing endometrial stripes or endometrial stripes greater than 5mm are suggestive of hyperplasia. Again, further diagnostic treatment with a D & C is necessary for complete resolution of this case.

#### 4.0 Conclusions regarding the Safety of Menostar® when treating osteoporosis in a postmenopausal with a uterus

Since the approval of Prempro® in 1994, the standard of care has been to combine and estrogen with a progestin to decrease the incidence of endometrial hyperplasia (with or without atypia) in an effort to decrease the well-documented risk of endometrial cancer produced when estrogen is given in an unopposed manner. Two documents were published, one in April 1994, entitled "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis" and a Guidance document was published in March 1995 entitled "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products use for Hormone Replacement Therapy of Postmenopausal Women." These documents outlined the recommendations for hormone therapy and combination hormone replacement trials relating to symptomatic indications, endometrial protection, and osteoporosis.

Osteoporosis is usually considered a life-time treatment because withdrawal of treatment usually results in bone loss that is more pronounced in the first few years after menopause and continues over the life of the woman. Therefore, if an unopposed estrogen treatment was used as the primary treatment, the endometrium must be protected against unopposed estrogen, even if the estrogen is considered a low dose in relationship to treatment of the bone. At one year the proliferation rate was 5.8% and at

two years the rate was 3.4%. It is unknown as to how many cases will progress to atypical hyperplasia, but in this trial the one case is worrisome, and fortifies the adage that proliferation in any postmenopausal female must be monitored and in some cases treated. As in this study, the general population should be monitored and treated according to the standards of the treating area.

#### Conclusion

In a Phase 3, randomized, double-blind placebo controlled study of two years duration one case of atypical endometrial hyperplasia was demonstrated. In addition, at one year of treatment the proliferation rate was 5.8% and at 2 years the proliferation rate was 3.4%. The endometrial hyperplasia and proliferation rates confirm the concept that unopposed estrogen, even if used at lower dosages, can predispose a patient to either a pre-malignant lesion or endometrial cancer if patients are not carefully followed. Patients should at a minimum be required to have an endometrial biopsy at one year (Novak's Gynecology, 13<sup>th</sup> edition, 2002); if the cervix is stenotic, a pelvic ultrasound that demonstrates an endometrial stripe of 3mm is more reassuring. Endometrial stripes of equal to or greater than 4mm (if a biopsy cannot be accomplished) may require treatment with a progestin. Biopsy is preferred because ultrasound does not address the endometrial proliferation that occurs and the possible need for a progestin.

#### Recommendation

If the primary medical reviewer assesses that Menostar™ is effective and safe for its intended use to treat osteoporosis, sponsor should adopt the initial paragraph in the Labeling Guidance to Industry published January 2004 in the Dosage and Administration section that recommends that in a woman with a uterus a progestin be used. If the sponsor does not adopt this initial paragraph in the estrogen label, the label should reflect the fact that endometrial biopsy is the preferred method to adequately assess the endometrium at one year intervals for any patient receiving unopposed estrogen. If an adequate endometrial biopsy can not be obtained a pelvic ultrasound should be performed and progestin use initiated. A treatment algorithm that includes intermittent use of a progestin may be appropriate for this product.

Phill H. Price, M.D.  
April 1, 2004

This review is 13 pages and a short addendum to the review is page 14.

### Addendum to Review

On March 25, I requested additional information on two patients, #400092 and #400038. The sponsor responded with the additional data. Patient 400092 did have successful endometrial biopsies at months 12 and 24. The uterus was entered and the histological result was normal with strips of benign surface and glandular lining epithelium and no endometrial polyp.

Patient 400038 had a normal screening biopsy that revealed strips of benign surface and glandular lining epithelium and an endometrial polyp on August 14, 2000. On August 27, 2001 an attempted endometrial biopsy was unsuccessful, therefore a transvaginal ultrasound was performed on August 29, 2001 with the result showing endometrial thickness of 4.9mm. The patient refused further a biopsy and discontinued the study medication on August 31, 2001.

The sponsor's response is adequate and no additional data is required.

In addition, on April 6, 2004 the sponsor submitted a proposed algorithm to be placed in the Dosage and Administration section of the label for Menostar™. This algorithm is meant as a guide to physician and patients in the most appropriate use Menostar™. In this proposal, as part of the continuing evaluation of expected bleeding, patients will stop use of Menostar™ and an endometrial biopsy will be performed.

As stated previously in the body of the review, the Guidance Document For Industry for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms of January 2004 does not recommend use of estrogen alone without concurrent use of a progestin (use of a progestin for 14 days has been shown to be efficacious). After consultation with gynecological sub-specialists in HFD-580, the consensus of the review team is progestin should be used at 6-month intervals for 14 days and an endometrial biopsy performed at yearly intervals. The rationale is even with combined or continuous estrogen plus progestin, the risk of endometrial hyperplasia is reduced to approximately 1% or less, but this reduction is not 0%. Therefore, the most comprehensive treatment and evaluation of patients receiving Menostar™ should involve a progestin and/or endometrial biopsy unless data can be produced that reveals no endometrial effect in this patient population after 3-5 years of treatment. This might be achieved with a Phase IV commitment.

In addition, on April 12, 2004 a second in-house consultation was sought and obtained from members of the reproductive team in HFD-580. The sponsor's proposed algorithm was explained and the opinion of the division is that estrogen, even when given in very low dosages to prevent osteoporosis, should have progestin treatment to negate the effect of unopposed estrogen on the endometrium. As an alternative, if the sponsor chooses not to adopt the class label for estrogen products, the sponsor should biopsy all patients with bleeding and all patients should be biopsied at one year intervals. If any proliferation is demonstrated with biopsy, that patient should be treated with a progestin.

*In summary, it is recommended that class labeling for estrogen and estrogen/progestin products be adopted for Menostar™. If the sponsor elects not to use estrogen class labeling, all bleeding should be investigated by biopsy and all patients should be biopsied at yearly intervals until long term safety data is obtained showing no proliferative effect upon the endometrium.*

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/s/

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Shelley Slaughter  
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I concur.

Daniel A. Shames  
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