CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-048

MEDICAL REVIEW

SEP 16 1999

Group Leader Memorandum

NDA:	**21-048**
Drug:	**®NAME** **17 β-Estradiol**
Indications:	**-Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause** **-Treatment of Vulval and Vaginal Atrophy**
Dose:	**0.050 mg/day (13.5 cm^2 patch)** **0.075 mg/day (20 cm^2 patch)** **0.10 mg/day (27 cm^2 patch**
Formulation:	**Transdermal Patch**
Applicant:	**Wyeth-Ayerst Research**
Original Submission:	**November 20, 1998**
10-Month Goal Date:	**September 20, 1999**
Date of Memorandum:	**September 7, 1999**

Background

There are a number of approved transdermal estrogen patches for the treatment of vasomotor symptoms in women. Some of these approved products are:

> Estraderm®: contains 17-β estradiol; designed to release 0.1 mg daily and 0.5 mg estradiol daily; applied by patients twice a week.
> Vivelle®: contains 17-β estradiol; designed to release 0 .0357 mg, 0.05 mg, 0.075 mg, and 0.1 mg of drug daily; applied by patients twice a week.
> Alora®: contains 17-β estradiol; designed to release 0.05, 0.075 and 0.10 mg of drug daily; applied by patients twice a week.
> Climara®: contains 17-β estradiol; designed to release 0.05, 0.075 and 0.10 mg of drug daily; applied by patients once a week.

The proposed product of this NDA review (referred to as E2-III TS) is also a trandermal estrogen patch and is applied once weekly. Three dosage forms are proposed for approval, and they are designed to release 0.05, 0.075, and 0.10 mg/day of estradiol, respectively. In essence, the proposed estrogen patch is most similar to Climara®. Wyeth Ayerst seeks two indications for their patch: treatment of vasomotor symptoms (VMS) and treatment of vulval/vaginal atrophy.

Summary of NDA Review

There were no chemistry issues raised during the review process. 17-β estradiol has a long history of use in both humans and animals transdermally, and thus there were no new preclinical studies performed for this application. The biopharmacology review focused on the pharmacokinetics with respect to the relatively long duration of action of this patch, which is designed to last a full 7 days before needing replacement. The biopharmacology reviewer concluded that the serum levels of estrogen absorption were acceptable, even extending out to day 7 of use.

I agree with the clinical reviewer that all 3 proposed doses of E2-III TS were effective in reducing vasomotor symptoms. Since all three doses were effective, it is reasonable to recommend starting at the lowest dose (0.05 mg) in product labeling.

I agree with the reviewer that all 3 proposed doses of E2-III TS were effective for treating vulvar-vaginal atrophy, based on demonstration of improvement in the vaginal epithelium maturation index. Ideally, studies to support the indication for treatment of vulval-vaginal atrophy should also include clinical data to support efficacy related to the symptoms of vaginal dryness, itching, and burning. However, I consider the data presented on vaginal epithelium maturation index (from two separate clinical trials) adequate to support this indication.

Overall, all three doses of E2-III TS appear to be well tolerated. Not unexpectedly, there is more vaginal bleeding and breast tenderness at increasing doses of E2-III TS. The highest dose of E2-III TS, in particular, leads to some concern regarding local skin tolerability and adverse effects on the endometrium. In Study 0802E1-316US, the percentage of patients reporting application site reactions was **10%** for the placebo group, **10%** for the 0.05 mg/day patch, **12%** for the 0.075 mg/day patch, and **21%** for the 0.10 mg/day patch. In this same trial, of 7 patients who withdrew from active treatment due to adverse events, 2 had application site reactions as their primary reason for withdrawal (both received 0.10 mg/day E2-III TS). Importantly, Study 0902E1-317 US, a similar study involving a similar number of subjects, did not demonstrate any particular concern regarding local skin tolerability with the 0.10 mg/day E2-III TS patch. This second study, however, raise concern about endometrial-related side effects, particularly again with the highest dose 0.10 mg/day patch. Two of the total 385 enrolled subjects in this latter trial experienced severe adverse events, and both of these subjects were in the 0.10 mg/day dosage arm. One subject was noted to have an enlarged uterus at study entry that rapidly enlarged further during the 12-week trial. Hysterectomy was performed 3 months after the trial, with pathology revealing uterine leiomyoma. The second subject had an end of study biopsy revealing endometrial hyperplasia, and was treated with progesterone for 10 days. A follow-up biopsy continued to reveal endometrial hyperplasia, and the patient was referred for appropriate treatment. Both of

these serious events were considered causally related to the increased estrogen exposure from the high-dose E2-III TS patch.

Conclusions

I agree with the approval of the E2-III TS patch at doses of 0.05, 0.075, and 0.10 mg/day for weekly use to treat VMS and to treat vulval-vaginal atrophy. All three doses have an acceptable risk/benefit profile. Dosing and Administration should recommend starting with the 0.05 mg/day patch for all patients, however, since higher estrogen exposures, particularly at the highest dose of 0.10 mg/day, may lead to more vaginal bleeding, breast tenderness, application site reactions, and adverse endometrial effects. The labeling, received by fax on 9/20/99 from Wyeth Ayerst, is acceptable.

Marianne Mann MD

Marianne ~~Mann~~, M.D. 9/20/99
Deputy Director, HFD-580

SEP 1 0 1999

Medical Officer's Original Summary of NDA 21-048

1. NDA 21-048
M O. Review

Submission Date: November 20, 1998
Review Completed: July 27, 1999

Drug name: 17 Beta Estradiol USP

Generic name: 17 β-Estradiol Transdermal System (E_2 III TS)

Proposed trade name:

Chemical name: Estradiol USP (estra-1,3,5,-(10)-trenen-3, 17β diol

Sponsor: Wyeth-Ayerst Research
P.O. Box 8299
Philadelphia, Pa 19101-8299

Phamacologic category: Estrogen

Proposed Clinical Indication:

Dosages and Route of Administration: 0.050, 0.075. 0.10 mg transdermally

NDA Drug Class: 5S

Related Drugs: Approved transdermal patches: Estraderm®, Climara®, Vivelle®, Alora®

Summary/Issues:

This 54-volume submission from Wyeth-Ayerst contains two well-designed placebo controlled studies to support a clinical indicatior The two estrogen deficiency states studied were relief of vasomotor symptoms and vulvar/vaginal atrophy. This is a 7-day patch that appears to sustain estradiol levels over the full 7 day treatment period from a clinical perspective, although, pharmacokinetic data suggests a gradual decrease release of estradiol over the 7-day period.

The two placebo controlled studies support the safety and efficacy of E_2 III TS over this 7-day treatment period. Adhesion appeared to be good during the fourth week of treatment cycle in the 13.5 cm^2 and 20 cm^2 patches, with lesser adhesion and more skin reactions in the 27cm^2 patch. In both studies the 27 cm^2 patch was associated with more common application site reactions such as pruritis and redness and a greater percentage (> 10%) of patch lift were reported in the 27 cm^2 patch.

Related Reviews: Statistical review dated:
Biopharm review dated:

2 Table of Contents:

3. Material Reviewed: Volumes 1.1 through 1.40

4. Chemistry/Manufacturing Controls: See Chemist review

5. Pharmacology/Toxicology: See Pharmacologist review

6. Clinical Background:

Estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. By direct action, it causes growth and development of the vagina, uterus, and fallopian tubes. With other hormones, such as pituitary hormones and progesterone, estradiol can cause enlargement of the breast through promotion of ductal growth, stromal development, and accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity or urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and the pigmentation of the nipples and genitals.

Loss of ovarian estradiol secretion after menopause can result in inability of thermoregulation causing hot flashes, associated with sleep disturbances and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

Orally administered estradiol is rapidly metabolized by liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. In contrast, the skin metabolizes estradiol only to a small extent. Transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates and require smaller doses than does oral therapy. Because estradiol has a short half-life (-1 hour), transdermal administration of estradiol allows a rapid decline in blood after systems are removed, e.g. in a cycling regimen.

6.1 Relevant human experience

Estraderm, in 1984, was the first transdermal patch approved in the US. Estraderm has an alcoholic reservoir. Newer estradiol patches (approved since 1994) are non-alcoholic matrix patches and appear to have less skin reaction than Estraderm. Additionally, newer matrix patches appear to have a more consistent release of estradiol over the treatment period. E_2 III TS is a 7-day patch, which is similar to the

7-day Climara® patch. Estradiol dosages are the same as Climara, that is, 0.50 mg, 0.75 mg, and 0.10 mg.

6.2 Important information from related INDs:

Clinical studies contained in this NDA were conducted under IND #44,168, submitted by Cygnus, Inc. on December 17, 1993. On November 9, 1995 Cygnus submitted a letter to the FDA stating that sponsorship of IND #44,168 had been transferred to Wyeth-Ayerst Laboratories.

6.3 Foreign experience:

This product has not been marketed in Europe or elsewhere. A supportive efficacy study was conducted in Europe under protocol 080-E1-330- EU.

6.4 Human Pharmacology, pharmacokinetics, and pharmacodynamics:

The delivery of estradiol in a transdermal delivery system, as opposed to oral administration, allows the estradiol to reach the circulation without undergoing first pass metabolism during intestinal absorption and in the liver to less active metabolites such as estrone and estriol. This permits the use of lower doses of estradiol delivered in a transdermal fashion to achieve the same pharmacologic result as an orally administered drug. Estradiol in blood is distributed between free estradiol, albumin bound estradiol, and sex hormone binding globulin (SHBG) bound estradiol.

Estradiol is transported across intact skin and into the systemic circulation by passive a passive diffusion process, the rate of diffusion across the stratum corneum being the principle rate controlling factor. The 17-ß-estradiol transdermal system (E_2 III TS) presents sufficient concentration of estradiol to the surface of the rate controlling skin to maintain continuous transport over the 7 days dosing period.

In a multiple-dose, randomized, crossover study, 28 postmenopausal women were treated for 2 weeks with two of the three doses of E_2 III TS (50, 75, or 100 µg/day). Each transdermal system was worn for 1 week (a total of 2 applications), with a 7-10-day washout period between doses. Tradename was applied to two sites on the abdomen. The pharmacokinetic parameters of serum estradiol unadjusted at week one were C_{avg} 37 ± 20 pg/ml for the 50 ug patch, C_{avg} 50 ± 29 pg/mL for the 75 ug patch, and 62 pg/ml ± 14 for the 100 ug patch.

The relative bioavailability of E_2 III TS at three different application sites was examined in a singe-dose (100 ug/day) study with 36 healthy, hysterectomized, postmenopausal women. In this randomized, crossover study, patches were applied to the lower abdomen, the outer aspect of the hip, and the upper quadrant of the buttock. The relevant pharmacokinetic parameters of serum estradiol (adjusted from baseline levels) are AUC_{168} and C_{avg}. The AUCs (pg/h/mL) for the studied sites are 11904 ± 4152 for the abdomen, 11127 ± 4299 for the hip, and 11506 ± 4704 for the buttocks; the C_{avg} (pg/mL) for the studied sites are 75 ± 25 for the abdomen, 70 ± 26 for the hip, and 72 ± 28 for the buttocks.

Comment: the 100 ug patch (27 cm^2) appears to be bioequivalent between the application sites of the buttocks, hip and abdomen. Similar results would be expected for the lower doses patches (50, 75 ug/day).

7 Description of clinical data sources

The sponsor conducted two adequate and well-controlled studies to support this NDA. Study 0802EI-316US was a randomized, double blind, placebo-controlled, parallel, multicenter study that enrolled 285 subjects at 23 sites. Two hundred sixty-three (263) subjects completed this study. Study 0802EI-317US was a randomized, double blind, placebo-controlled, parallel, multicenter study that enrolled 385 subjects at 28 sites. Three hundred fifty-five subjects (355) completed this study. This study also had an open-label Climara® arm, which was used for descriptive purposes. Of note, FDA requirements for the VMS indication could be met by a single placebo-controlled study.

8 Clinical Studies

Study 0802E1-316-US

8.1.1

The primary objective of this study was to compare the efficacy and safety of three different dosages of a 7-day 17ß-estradiol (E_2) patch compared with a placebo patch for the relief of vasomotor symptoms and atrophic vaginitis associated with the menopause. Secondary objectives were to assess the effects of the E_2 patch on quality-of-life indicators and to examine population pharmacokinetics of the E_2 patch. Evaluations of patch adhesion and skin irritation were also conducted.

8.1.2 Design

This was a twelve-week, double blind, multiple dose, randomized, placebo-controlled, parallel multi-center study.

8.1.3 Source and number

The study plan called for enrolling 304 subjects in order to complete approximately 200 patients. There were 285 subjects enrolled at 23 sites and 263 subjects completed the study; 68 to 73 patients were enrolled in each of the 4 treatment groups.

Inclusion Criteria:

Subjects could be enrolled in the study if they satisfied the following inclusion criteria:

- Healthy, postmenopausal women from 40 to 65 years of age;
- Last natural menstrual cycle completed at least 6 months before baseline screening **–or-** the patient had a bilateral oophorectomy at least 2 months before baseline screening;
- Hormone levels:
  1) If the last menstrual cycle occurred less than 12 months before baseline screening, the plasma E_2 had to be $\leq$ 20 pg/mL ($\leq$73.42 pmol/L), and FSH concentration had to be $\geq$ 50 IU/L.
  2) If the last menstrual cycle occurred 12 months or more before baseline screening, the FSH concentration had to be greater than the lower limit for postmenopausal women for the given laboratory.
- Minimum of 7 moderate to severe hot flushes per day or an average of 60 per week. A moderate hot flush was defined as a warm sensation with sweating that does not disrupt activity. A severe hot flush is defined as a hot sensation with sweating that disrupts activity. (A mild flush was defined, as a fleeting warm sensation without sweating that does not disrupt activity).
- Patients could be no more than 35% above the ideal body weight using the normograph for body mass index. (When the study was initiated the upper limit was + 20%; however, to increase enrollment and to more adequately reflect the body mass index of menopausal women, the protocol was amended during the study to change the upper limit to + 35% of ideal body weight.
- In the opinion of the investigator, sufficient intelligence and motivation for the subject to continue through the study to its completion.
- Patients had to sign an informed consent form.

Exclusion Criteria:

A history or active presence of any of the following prevented enrollment:

- Hypersensitivity to estrogens or adhesives;
- Use of estrogen, progestin, or androgen-containing medication within 8 weeks for oral therapy or 4 weeks for transdermal therapy before baseline screening. Patients receiving estrogens, progestins,

or androgens by routes of administration other than oral or transdermal (e.g. intramuscular) had to be individually approved for study inclusion by the medical monitor;

- Use of the following medications within 2 weeks of prestudy screening:
  Dopaminergic or antidopaminergic drugs,
  Clonidine,
  Digitalis preparations
  Anticonvulsants (phenytoin, phenobarbital, chronic use of any phenobarbital-based medication)
  Bellergal or similar products containing belladonna alkaloids, ergotamine tartrate, or phenobarbital
  Regular use (more than twice per week) of psychotropic medication, including antidepressants, hypnotic sedatives, and tranquilizers;
- Thrombophlebitis, thrombosis, or thromboembolic disorders related to estrogen;
- Myocardial infarction or ischemic heart disease;
- Chronic renal or hepatic disease;
- Cerebrovascular accident, stroke, or transient ischemic attack;
- Known or suspected estrogen-dependent neoplasia;
- Endometrial hyperplasia;
- Gallbladder disease (patients who had a cholecystectomy could be enrolled;
- Neuro-ocular disorders, e.g. retinal vasculitis;
- Undiagnosed abnormal genital bleeding within 12 months of screening;
- Use of an intrauterine device within 3 months of screening;
- History of malignancy with the exception of basal cell carcinoma of the skin.

The **Active** presence of the following also prevented enrollment:

- Skin disease of the abdomen requiring therapy or, in the opinion of he investigator, potentially interfering with study patch evaluation;
- Elevated sitting blood pressure (>160 mm Hg systolic or > 90 mm Hg diastolic); Patients could not be using more than two anti-hypertensive medications per day;
- Clinically significant abnormal liver function test results, i.e. greater than 1.5 times upper limit of normal;
- Endocrine disease except for controlled thyroid disease;
- Any malignancy with the exception of basal cell carcinoma of the skin;
- Thrombophlebitis, thrombosis or thromboembolic disorders;
- Smoking more than 15 cigarettes a day;
- Known substance abuse (alcohol or drug);
- Inability to perform an endometrial biopsy in patients with a uterus;
- Evidence of malignant changes on the prestudy mammogram;
- Fasting total cholesterol >7.76 mmol/L (300 mg/dL) or triglycerides > 3/39 mmol/L (300 mg/dL);
- Fasting glucose >7.77 mmol/L (140 mg/dl);
- Any Bethesda System report of squamous intraepithelial lesions (SIL) or greater.

Comment: Inclusion and exclusion criteria were appropriate for this study.

Patients could be withdrawn from the study if they did not use the patch for intervals longer than 96 continuous hours in any one-week, or a total of 144 discontinuous hours in any consecutive cycles.

Study Procedures:

At screening visits 1A and 1B a complete medical history, including significant medical history (system/disease/disorder), surgery upon reproductive and/or endocrine organs, last natural menstrual period, and obstetrical history was recorded during Visit 1A. Additional demographic information was collected including smoking behavior for the most recent 3 months, history of alcohol consumption, and race. For patients requiring an 8-week washout period from oral estrogen, progestin, or androgen therapy, the medical history and obstetrical history was taken during Visit 1A; Visit 1B will take place at

least 8 weeks later. For patients requiring a 4-week washout period from transdermal estrogen therapy, the medical and obstetrical history took place at Visit 1A; Visit 1B was at least 4 weeks later. **If no washout period was required, Visits 1A and 1B were combined.**

During visit 1B, all patients, including those who had completed the required washout period, were given a daily diary card to maintain for at least 14 consecutive days before entry into the study. The number and severity of hot flushes, concomitant medications and other symptomatology were recorded for each 24-hour period. One day, pocket-sized cards (pocket prompts) were provided to record the frequency and severity of the flushes at the time they occurred. The total number of mild, moderate, and severe flushes in each calendar day were transcribed by the patient from each pocket prompt onto the daily diary card. The diary was returned to the investigator at Visit 2. If the patient experienced at least 7 moderate to severe flushes or greater per day or an average of 60 each week over the 2-week screening period for baseline flushes, the screening process continued. These data were be entered on the case report form (CRF) and the diary cards remained at the study site.

At Visit 2 the baseline diary cards were collected and the number of flushes over the 14-day period (a total of at least 7 moderate to severe hot flushes per day or and average of 60 per week) were documented. Each week of the 2-week screening period was considered independently. If the criteria were not met, the patient could not continue in the study. During this visit the following procedures were completed:

- Complete physical examination including blood pressure;
- General condition of the skin;
- Height and weight were measured and the Nomograph for body mass Index was completed;
- A breast examination, a pelvic examination (including a cervical and vaginal cytologic smear with vaginal maturation index) and an endometrial biopsy for patients with a uterus was performed. All patients with hyperplasia were excluded.
- Laboratory safety screen was performed including hematology, blood chemistry (after a 12-hour fast), and urinalysis;
- Samples of serum FSH and estradiol concentration determinations for screening were collected;
- A Mammography was done if the patient had not had a previous mammogram within 6 months of visit 2;
- A Quality of Life Questionnaire was completed by each patient;
- All baseline studies must be completed within 3 months of randomization or be repeated if more than 3 months before randomization (Visit 3);
- All data was recorded on the case report forms
- The investigator maintained a screen log for all patients who were screened, and it contained the following information: patient number, initials, date, reason(s) for screen failure, and race. It was essential for those patients who fail screening (i.e. patients who sign an informed consent form and fail inclusion and/or exclusion criteria) be recorded on the screen log along with the reason(s) for the screen failure. The presence of inclusion criteria and the absence of exclusion criteria were verified on the case report form.

Visit 3 initiated cycle 1 and occurred as soon as laboratory results were available. The results of the history and physical examination were checked and all laboratory reports including mammography, endometrial biopsy, and vaginal maturation index results from visit 2 were reviewed. The prestudy daily diary cards were reviewed for at least 14 days, and the investigator determined whether the patient met the hot flush criteria for study inclusion. For women whose last menstrual period occurred 12 months or longer before baseline screening, the FSH level had to be greater than the lower limit for postmenopausal women for the given laboratory. For women whose last menstrual period occurred less than 12 months before the baseline screening, estradiol levels had to be $\leq$ 20 pg/mL and FSH levels had to be $\geq$ 50 mIU/mL. Additionally, the general condition of the abdomen was again examined to document the absence of skin pathology. Weight, blood pressure and pulse were recorded. Blood samples for population pharmacokinetic analysis was collected before patch application. Results of the analyses were blinded throughout the study. The baseline Quality of Life Questionnaire was completed.

Patients were then assigned a randomization number and were provided with a 5-week supply of study medication, five daily diary cards, and pocket prompts. Medication was provided for one 28-day cycle. An additional diary card and patch was supplied in case of loss or damage, or if the patch falls off. Patients were given written instructions for applying patches. Patients were instructed to apply one patch to the abdomen each week at the same time at the beginning of each study week. The date and time of patch application was noted on the diary card for inclusion on the CFR. Upon completion of 1 week of therapy, the patient applied a new patch to a different site on the abdomen with no interruption of therapy. Should a patch become loosened or detach during the wear period, an attempt was made to reapply the patch to the same site. If the patch did not remain adherent, a new patch was applied to the same site for the remaining days of the week with no change in the patch wear schedule. If patch non-use intervals exceeded 4 consecutive days (96 hours) in any one-week, or a total of 144 discontinuous hours in any cycle, the patient was withdrawn from the study.

Visit 4 took place during days 24-28 of cycle 1. The visit took place before the patch was changed. Weight, blood pressure and pulse were obtained. The condition of the abdominal skin (exclusive of the latest patch site) was evaluated and scored by the investigator, and the data was entered on the CRF at the end of the 28-day cycle, using a modified Draize scale.

Visit 5 took place as close as possible to day 29 of cycle 2, but took place before patch removal for patients wearing the investigational patch. Study procedures conducted were the same as in visit 4. Patients rated the intensity of itching/pruritis during the previous 28 days and the investigator recorded the results on the CRF. Unused patches were collected and additional patches were dispensed.

Every effort was made to schedule the final visit (Visit 6) on day 29 of cycle 3. Under exceptional circumstances, this visit may take place within 7 days before day 29. In either case, the visit was to be scheduled before the patch was removed. A physical examination, blood pressure and pulse, weight, gynecologic examination, vaginal cytologic smear with vaginal maturation index, endometrial biopsy (as appropriate), and laboratory assessments were completed. A third Quality of life Questionnaire and a Patch Wear Evaluation was completed. The condition of the abdominal skin, exclusive of the latest patch site, was evaluated by the investigator and scored. All patients rated the intensity of itching/pruritis during the previous 28 days and the investigator recorded the results on the CRFs. Patients were to continue therapy until the completion of cycle 3, at which time the study coordinator would arrange collection of the final diary card, all unused patches, and completion of the QOL Questionnaire and Patch Wear Evaluation. In addition, *before patch removal,* blood samples for pharmacokinetic analysis were collected from *all* patients. Blood collection for pharmacokinetic analysis took place as close as possible to 168 hours (7 days) following the last patch application.

8.1.3.2

Efficacy

A one-way analysis of variance was used to compare efficacy evaluations (change from baseline to the end of each treatment evaluation period in the average daily number and severity of flushes) among treatment groups. Multiple comparisons of active patches versus placebo were made through a protected least significant difference approach. A 95% confidence interval of the mean changes from baseline for all study groups is provided. If the sample size per site was sufficient, a two-way analysis of variance with the study site as factor was used.

The primary efficacy parameters were a) frequency of hot flushes and b) intensity of hot flushes. The baseline of flushes was considered to be the average daily number of flushes reported during the 14-day screening period. Baseline and weekly averages were calculated as the arithmetic mean of the daily totals. The severity of each flush was recorded as mild (1), moderate (2), and severe (3). Average baseline severity was computed during the 14-day screening period was calculated as the arithmetic mean of the daily weighted severity score.

A secondary endpoint included the influence of estrogen on the vaginal mucosa, which identified a change in the proportion of vaginal epithelial cells (vaginal maturation index) before study onset and at the end of the third 28-day cycle. Additionally, the influence of estrogen therapy on the QOL was assessed as a secondary endpoint, through identification of changes using a QOL questionnaire at baseline compared to the end of the third 28-day cycle. The Patch Wear Evaluation was assessed at the end of the study, and evaluated patient tolerability of this 7-day patch.

Other laboratory determinations obtained included routine blood sampling, urinalysis, estradiol and FSH levels which were obtained at prestudy and visits 3 and 6, serum samples for population pharmacokinetic analysis, vaginal and cytologic smears, an endometrial biopsy and a prestudy mammography, if necessary. The population pharmacokinetic analysis included serum estradiol, estrone and estrone sulfate. These serum samples were sent to a separate laboratory for analyses.

Safety

The safety analyses were based on clinical reports of AEs (such as skin irritation) and laboratory values. irritation. All patients who entered the drug administration period were included in the analysis of safety. Mean changes in clinical safety variables (blood pressure, weight, and endometrial biopsy) and laboratory data (chemistry and hematology) are presented in a series of tables. Any patient demonstrating hyperplasia (based on the agreement of two primary study pathologists) at the end of the study were given appropriate treatment. Local skin application site reactions were rated by the patient and recorded by the investigator at Visits 4, 5, and 6. The investigator also routinely assessed Patch adhesion at Visits 4, 5, and 6.

8.1.3.3 Analyses

There is large variability within and between patients, and differences across study sites are to be expected because of the subjectivity of the parameter. Based on data for the change in the mean number of frequency of flushes after treatment with Climara®, a standard deviation of approximately 23 was observed. A difference of 16 flushes per week in the mean number of reductions between the active treatment groups and the placebo group is considered meaningful. With approximately 50 patients per treatment group, the study has a 90% power to detect such a difference. An evaluable patient is one who has completed at least 28 days of treatment and provided a daily diary card for the same period.

8.1.4 Results

The table 1 (sponsor's table 8.1.1) shows the disposition of all patients included in the analyses of safety and efficacy:

Table 1

	E_2 III TS 13.5 cm^2	E_2 III TS 20 cm^2	E_2 III TS 27 cm^2	Placebo	Total
Safety (all enrolled)	N = 71	N = 73	N = 68	N = 73	285
Intent-to –treat[a]	70 (99%)	73 (100%)	68 (100%)	71 (97%)	282 (99%)
Efficacy-evaluable[b]	64 (90%)	60 (82%)	61 (90%)	64 (88)	249 (87%)

[a] Three patients received treatment and had baseline flush data; however, no on-therapy flush data were available.

[b] These patients met all the criteria to be excluded in the efficacy-evaluable analysis; however, they could still have some symptom data excluded in the latter part of the study.

Table 2 (sponsor's table 8.1.2) summarizes the primary reasons for discontinuations by treatment group and overall.

Table 2

Table 2 shows the primary reasons for discontinuation, Number (%) of patients

	E_2 III TS 13.5 cm^2	E_2 III TS 20 cm^2	E_2 III TS 27 cm^2	Placebo All 3 Sizes
Enrolled	N = 71	N = 73	N = 68	N = 73
Any reason	7 (10%)	2 (3%)	5 (7%)	8 (11%)
Adverse reaction	2(3%)	2 (3)	2 (3%)	0
Failed to return	2 (3%)	0	2 (3%)	1 (1%)
Other medical event	1 (1%)	0	0	0
Other non-medical event	0	0	0	1 (1%)
Patient request	0	0	1 (1%)	0
Protocol violation	1 (1%)	0	0	0
Unsatisfactory efficacy response	1 (1%)	0	0	6 (8%)
Total Discontinued	7 (10%)	2 (3%)	5 (7%)	8 (11%)

Note: Overall, 22 (8%) of enrolled patients discontinued from the study prematurely. Of that small number of patients, the majority discontinued either because of an adverse event (all in the active treatment arms) or an unsatisfactory efficacy response (mostly in the placebo arm). The primary reasons for withdrawal due to an AE in the active treatment arm included application site reactions, edema, pain and depression.

Twenty-three (23) patients in the four treatment groups were allowed to remain in the study despite having insufficient baseline flush data. Two (2) patients were in the E_2III TS 13.5 cm^2 group, 10 were in the E_2 III TS 20 cm^2 group, 6 were in the E_2 III TS 27cm^2 group, and 5 were in the placebo group. An additional 18 patients were allowed to remain in the study despite inclusion criteria violations. Of these violations, 10/18 were either E_2 levels which were too high for patients with a menstrual cycle less than 12 months, or FSH levels which were too high; or if the menstrual cycle was greater than 12 months, FSH levels which were too low. Thirty-two (32) patients took prohibited medications during the study. The majority of these drugs were antiepileptic, psychotropic, chronic antihistamines, corticosteroids for > 10 days, narcotic analgesics and one patient who took Estrace ®. This patient, who was enrolled in the placebo group, number 31603-0042, was later withdrawn from the study.

The majority of patients in this study took some type of concomitant medications during treatment. The most common types of concomitant therapy fell under the following categories: other analgesics and antipyretics, nonsteroidal anti-inflammatory and anti-rheumatoid products, and multivitamin combinations.

Most patients complied with the study treatments; eleven (11) patients had flush data excluded because of noncompliance with patch wear. Some patients had time intervals of 2 weeks excluded, but it was possible for a patient to still have sufficient data for each week. Three (3) patients had one full week of data excluded from the efficacy analysis because of lapses in patch use; they were patients 31605-0013 (13.5 cm^2), 31618-0004 (20 cm^2) and patient 31614-0030 in the placebo group.

Comment: Twenty-three patients were allowed to remain in the study despite mean flush data of < 60 flushes per week. Since the baseline mean flush data was balanced and ranged from 12.1 to 13.3 treatment groups, this is not felt to be a major concern.

The sponsor presented baseline demographic information for all patients in table 2A. Due to the size of this table, information will be summarized. The mean age was approximately 52 for all treatment groups. Ethnic origin in this study revealed 91% of the patients were White, 5% Black, 3% Hispanic, < 1% Native American, and 1% Other. The treatment groups were comparable as to height, with a mean height of 162.7 cm; treatment groups were comparable as to weight, with a mean of 67.3 kg; and treatment groups were comparable as to a mean to Body Mass Index of 25.3 kg/m^2 . Sixty-seventy percent (67%) of patients had a natural menopause, with a high of 70% in the 20 cm^2 group and a low of 59% in the 13.5 cm^2 group; thirty-three per cent (33%) had a surgical menopause, with a high of 41% in the 13.5 cm^2 group and a low of 30% in the 20 cm^2 group. Forty-seven percent (47%) of patients has had a hysterectomy and 53% did not have a hysterectomy. The treatment groups were also comparable in their non-use of cigarettes, with 73% being non-smokers. The exception to comparability was in the use of alcoholic beverages, where there was a significant difference among groups. Pair-wise comparisons using Fisher's exact test showed significant differences between the E_2 13.5 cm^2 and placebo groups ($p = 0.0023$) and between the E_2 20 cm^2 and placebo groups ($p = 0.009$) (with more alcohol intake in the active treatment arms vs. the placebo arm).

Efficacy

The ITT population included all patients randomized in the study who applied at least one patch and had at least 1 day of diary flush data for any week while on treatment. These patients were included in the analysis for the week that they participated. Patients who applied a patch but had no diary flush data available for that week were not included in the analysis for that week.

Table 3 shows the analysis of the mean daily number of hot flushes for the ITT population. This table is modified from the sponsor's table 4 and shows weeks 1 through 4 of treatment and weeks 8 and 12 of treatment.

MEAN DAILY NUMBER OF HOT FLUSHES, ITT POPULATION
STATISTICAL ANALYSIS

Time Period Parameter	E_2 III TS 13.5 cm^2	E_2 III TS 20 cm^2	E_2 III TS 27 cm^2	Placebo
Total no. of patients	*70*	*73*	*68*	*71*
Week 1				
No. of patients	70	73	67	71
Baseline mean ± SD	12.1 ± 3.8	12.8 ± 5.5	12.3 ± 5.1	12.5 ± 4.2
Therapy mean ± SD	8.8 ± 5.8	8.2 ± 5.9	7.0 ± 4.2	8.1 ± 4.3
Mean change ± SE	-3.4 ± 0.5	-4.6 ± 0.5	-5.3 ± 0.6	-4.4 ± 0.5
Mean % change ± SE	-30.1% ± 4.5	-36.7% ± 3.5	-41.0% ± 3.9	-33.6% ± 3.8
Week 2				
No. of patients	68	73	68	71
Baseline mean ± SD	12.1 ± 3.8	12.8 ± 5.5	12.3 ± 5.1	12.5 ± 4.2
Therapy mean ± SD	6.5 ± 5.0	6.2 ± 5.5	4.5 ± 3.8	7.3 ± 4.5
Mean change ± SE	-5.6 ± 0.5	-6.5 ± 0.5	-7.7 ± 0.6*	-5.2 ± 0.6
Mean % change ± SE	-48.8% ± 4.0	-53.1% ± 3.6	-63.0% ± 3.4	-39.5% ± 4.3
Week 3				
No. of patients	68	72	68	71
Baseline mean ± SD	12.1 ± 3.8	12.8 ± 5.5	12.3 ± 5.1	12.5 ± 4.2
Therapy mean ± SD	5.5 ± 4.9	5.3 ± 5.3	3.5 ± 3.8	7.0 ± 4.7
Mean change ± SE	-6.6 ± 0.5	-7.5 ± 0.5*	-8.8 ± 0.6*	-5.5 ± 0.6
Mean % change ± SE	-57.5% ± 4.2	-60.0% ± 3.9	-72.1% ± 3.4	-42.5% ± 4.3
Week 4				
No. of patients	67	71	68	71
Baseline mean ± SD	12.2 ± 3.8	12.9 ± 5.6	12.3 ± 5.1	12.5 ± 4.2
Therapy mean ± SD	4.6 ± 4.4	4.6 ± 5.1	3.0 ± 3.6	6.8 ± 4.6
Mean change ± SE	-7.6 ± 0.5*	-8.2 ± 0.5*	-9.3 ± 0.6*	-5.7 ± 0.6
Mean % change ± SE	-64.8% ± 3.9	-65.8% ± 3.8	-76.6% ± 3.4	-44.2% ± 4.4
Week 8				
No. of patients	64	70	64	67
Baseline mean ± SD	12.0 ± 3.7	12.8 ± 5.6	12.3 ± 5.2	12.3 ± 4.0
Therapy mean ± SD	2.8 ± 3.9	2.7 ± 5.1	2.0 ± 2.9	6.0 ± 4.6
Mean change ± SE	-9.2 ± 0.5*	-10.2 ± 0.5*	-10.3 ± 0.6*	-6.3 ± 0.6
Mean % change ± SE	-78.7% ± 3.4	-81.9% ± 2.8	-84.5% ± 2.8	-49.8% ± 4.6
Week 12				
No. of patients	62	70	60	63
Baseline mean ± SD	12.0 ± 3.7	12.8 ± 5.6	12.2 ± 5.1	12.5 ± 4.1
Therapy mean ± SD	1.9 ± 3.4	2.0 ± 3.5	0.9 ± 1.9	6.0 ± 5.0
Mean change ± SE	-10.1 ± 0.4*	-10.8 ± 0.6*	-11.2 ± 0.7*	-6.5 ± 0.7
Mean % change ± SE	-86.0% ± 2.8	-85.2% ± 2.9	-91.9% ± 2.3	-50.3% ± 5.4

* Significant differences in mean changes between each active patch group and the placebo patch group (p-values < 0.05).

Note at week two the E_2 III TS 27 cm^2 patch was significantly different from placebo; at week 3, both the E_2 III TS 20 cm^2 and the 27 cm^2 patches were significantly different from placebo; by week 4 all treatment groups were significantly different from placebo at the p= 0.05 level. This statistical difference was maintained at weeks 8 and 12. Of note is the high response of 49.8% in placebo by week 8 and this is maintained until week 12, showing the high placebo effect usually seen in VMS studies. The sponsor also submitted analysis with the efficacy-evaluable population. Approximately 58 patients were excluded for various reasons during this 12-week study. Analyses from the efficacy-evaluable patients showed similar results to the ITT analyses.

Table 4 shows the analysis of the mean severity of hot flushes for the ITT population. This is modified from the sponsor's table 6. As in the VMS frequency analysis weeks 1 through 4 will be shown, followed by weeks 8 and 12. The severity of each hot flush was recorded as mild (1), moderate (2), or severe (3). The average baseline severity was computed during the 14-day screening period and was calculated as the arithmetic mean of the daily weighted severity score.

Table 4 (sponsor's table 6)

MEAN SEVERITY OF HOT FLUSHES, ITT POPULATION
STATISTICAL ANALYSIS

Time Period Parameter	E_2 III TS 13.5 cm^2	E_2 III TS 20 cm^2	E_2 III TS 27 cm^2	Placebo
Total no. of patients	*70*	*73*	*68*	*71*
Week 1				
No. of patients	70	73	67	71
Baseline mean ± SD	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3
Therapy mean ± SD	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5
Mean change ± SE	-0.2 ± 0.1	-0.2 ± 0.0	-0.2 ± 0.1	-0.1 ± 0.0
Mean % change ± SE	-10.1% ± 2.4	-8.9% ± 1.7	-8.8% ± 2.7	-6.3% ± 2.1
p-Value	< 0.001	< 0.001	0.001	0.002
Week 2				
No. of patients	68	73	68	71
Baseline mean ± SD	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3
Therapy mean ± SD	1.9 ± 0.7	1.9 ± 0.7	1.7 ± 0.8	2.0 ± 0.6
Mean change ± SE	-0.5 ± 0.1	-0.4 ± 0.1	-0.6 ± 0.1*	-0.2 ± 0.1
Mean % change ± SE	-19.5% ± 3.5	-17.7% ± 3.1	-27.4% ± 4.2	-10.6% ± 2.8
Week 3				
No. of patients	68	72	68	71
Baseline mean ± SD	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3
Therapy mean ± SD	1.6 ± 0.8	1.7 ± 0.7	1.5 ± 0.9	2.0 ± 0.6
Mean change ± SE	-0.7 ± 0.1*	-0.6 ± 0.1*	-0.8 ± 0.1*	-0.3 ± 0.1
Mean % change ± SE	-29.3% ± 4.2	-24.3% ± 3.2	-33.9% ± 4.4	-14.2% ± 2.9
Week 4				
No. of patients	67	71	68	71
Baseline mean ± SD	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3
Therapy mean ± SD	1.5 ± 0.9	1.5 ± 0.8	1.3 ± 1.0	1.9 ± 0.7
Mean change ± SE	-0.8 ± 0.1*	-0.7 ± 0.1*	-1.0 ± 0.1*	-0.3 ± 0.1
Mean % change ± SE	-34.2% ± 4.5	-31.9% ± 3.9	-44.2% ± 5.0	-14.6% ± 3.2
Week 8				
No. of patients	64	70	64	67
Baseline mean ± SD	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3
Therapy mean ± SD	1.2 ± 0.9	1.2 ± 0.9	1.0 ± 0.9	1.8 ± 0.7
Mean change ± SE	-1.1 ± 0.1*	-1.0 ± 0.1*	-1.3 ± 0.1*	-0.5 ± 0.1
Mean % change ± SE	-46.8% ± 5.2	-44.8% ± 4.7	-56.9% ± 5.1	-20.9% ± 3.4
Week 12				
No. of patients	62	70	60	63
Baseline mean ± SD	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3
Therapy mean ± SD	0.9 ± 0.9	1.0 ± 0.9	0.7 ± 0.8	1.8 ± 0.8
Mean change ± SE	-1.4 ± 0.1*	-1.2 ± 0.1*	-1.7 ± 0.1*	-0.5 ± 0.1
Mean % change ± SE	-60.3% ± 4.9	-54.5% ± 4.9	-70.6% ± 4.8	-20.2% ± 4.6

* Significant differences in mean changes between each active patch group and the placebo patch group (p-values < 0.05).

Note at week 2, the E_2 III TS 27 cm^2 patch was significantly different from placebo; at week 3 all three patches were significantly different from placebo. This trend continued thorough the first treatment cycle and through cycles 2 and 3.

As an objective parameter, the sponsor studied the vaginal maturation index. The maturation index is the relative ratio of basal/parabasal cells, intermediate cells, and superficial cells evaluated from vaginal smears taken at screening (baseline) and at week 12. The results showed that the percentage of vaginal superficial cells increased significantly from screening values and the percentage of vaginal parabasal cells decreased from screening in all three active E_2 groups. The mean increases from screening for superficial cells were 10.3%, 17.3%, and 19.2% for the 13.5 cm^2, 20 cm^2, and 27 cm^2 treatment groups, respectively. The mean decrease from screening for parabasal cells were 16.9%, 15.2% and 22.4% for the 13.5 cm^2, 20 cm^2, and 27cm^2 treatment groups, respectively. In the placebo group, the mean changes from screening were not significant for any of the cell types.

Comment: These findings support the biologic effect of this estradiol patch on the vaginal epithelium and supports the indication of treatment of vaginal atrophy.

The sponsor also studied two quality-of-life questionnaires, the SF-36 and the WHQ. The analyses in these tables represent patients who completed questionnaires both at baseline and on therapy. In the SF-36 questionnaire, the scores for the first eight subscales ranges from 0 to 100 and increases in the subscale scores indicate improvements. However, for the health transition question, the scale ranges from 1 to 5 and a decrease indicates improvement. In the WHQ, the scores ranges from 0 to 1 for each subscale and decrease in the subscale scores indicate improvement. In 3 of 8 subscales, vitality, social functioning and mental health there was significant changes reported for all three patches. In another subscale, role-emotional, values increased significantly in the 20 and 27 cm^2 groups. Other subcales showed improvement from baseline, but not to a significant level.

In the WHQ questionnaire, scores decreased from baseline to the end of therapy, which indicated improvement. There were significant changes from baseline in all three patches for six of nine subscales—depressed mood, memory/concentration, sexual behavior, sleep problems, somatic symptoms, and vasomotor symptoms. For subscales of sleep problems, somatic symptoms, and vasomotor symptoms, the placebo group also had significant changes from baseline. In summary, both questionnaires demonstrated that many of the patients' symptoms were improved while on therapy.

Safety

All adverse events were recorded. Adverse experiences were classified into a standardized terminology using the COSTART (Coding Symbols for Thesaurus of Adverse Reactions Terms), by body system. All tabulations are of the number of patients reporting a specific event, not the number of events reported. Patients who had more than one particular event are therefore counted only once in the overall (any) category for event, within that body system.

All patients who took medication are included in the safety analysis. Two hundred eighty-five (285) patients were exposed to at least a single patch; 212 patients were exposed to E_2 III TS and 73 received placebo patches. The sponsor presented table 10.1A. Table 10.1A reported that at the end of the twelfth treatment week, 253 patients remained in the study.

Data for adverse experiences were analyzed using the treatment emergent adverse events (TEAEs). TEAEs were events not present at baseline or events present at baseline that worsened during treatment. Descriptive tables 10, 11, and 12 summarized the incidence, severity and relationship to treatment, and body systems. Overall, in table 10, 226 (79%) patients in the four treatment groups reported systemic adverse events. In the 13.5, 20, and 27 cm^2 treatment groups, 56 (79%) patients, 59 (81%) patients, and 58 (85%) patients, respectively, reported adverse events. In the placebo groups, 53 (73%) patients reported adverse events.

Sponsor's table 10 reported TEAEs of 3% or more by any treatment group. This reviewer will report TEAEs experienced by at least 5% of patients per treatment arm. The TEAEs were grouped by body system. It should be noted that body system totals were not necessarily the sum of the individual study events since a patient could report two or more different study events in the same body system. Table 10 will now be summarized in a descriptive fashion due to the size of this table. **Under Body as a Whole**, headache was the most common adverse event reported. It was reported in 16 (22%) of the placebo group, and in 23 (32%), 20 (27%) and 16 (22%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Pain was reported in 28 (10%) of patients in the placebo group and in 8 (11%), 5 (7%), and 5 (7%) of patients in the 13.5, 20, and 27 cm^2 groups, respectively. Abdominal pain was reported in 2 (3%) of placebo patients and in 5 (7%), 6 (8%), and 2 (3%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Back pain was reported in 4 (6%) of patients in the placebo group and in 7 (10%), 7 (10%), and 7 (10%) of patients in the 13.5, 20, 27 cm^2 E_2 III TS groups, respectively. **Under Digestive system**, nausea was reported in 6 (8%) of patients in the placebo group, and in 8 (11%), 6 (9%) and 2 (3%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Diarrhea was reported in 4 (5%) of patients in the placebo group, and in 4 (6%), 3 (4%) and 2 (3%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Dyspepsia was reported in 2 (3%) of placebo patients and in 4 (6%), 6 (8%), and 2(3%) of patients in the 13.5, 20, and 27.5 cm^2 E_2 III TS groups, respectively.

Under Musculoskeletal system, arthralgia was reported in 3 (4%) of patients in the placebo group, and in 3 (4%), 2 (3%), and 5 (7%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups respectively. **Under Nervous system**, insomnia was reported in 7 (10%) of placebo patients, and in 3 (4%), 2 (3%), and 2 (3%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. **Under Respiratory system**, pharyngitis was reported in 8 (11%) of patients in the placebo group, and in 1 (1%), 4 (5%), and 8 (12%) of patients in the 13.5, 20, 27 cm^2 E_2 III TS groups, respectively. Rhinitis was reported in 7 (10%) of patients in the placebo group, and in 9 (13%), 3 (4%), and 5 (7%) of patients in the 13.5, 20, and 27 cm^2 groups, respectively. **Under Skin and Appendages**, application site reactions were reported in 7 (10%) of patients in the placebo group, and in 7 (10%), 9 (12%), and 14 (21%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. **Under Urogenital system**, breast pain was reported in 2 (3%) of patients in the placebo group, and in 9 (13%), 9 (12%), and 14 (21%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Vaginitis was reported in 2 (3%) of patients in the placebo group, and in 2 (3%), 8 (11%) and 2 (3%) of patients in the 13.5, 20, and 27 cm^2 groups respectively.

Comment: Both the types and incidence of TEAEs reported in this study are consistent with experience with other transdermal patch studies. In other studies and this study, headache, breast pain (usually increasing with increased estrogen dose), application site reactions, and either pharyngitis or rhinitis were shown to be the most common AEs. The only AE in this study to demonstrate dose responsiveness was application site reactions.

There were no deaths reported in this study.

Two patients (31614-0039 and 31617-0006, both in the 13.5 cm^2 treatment group) were initially reported as having severe adverse events detected during the physical examination at the end of the study. Patient 31614-0039 had fibrocyst of the left breast that, upon additional investigation, was reduced in size, not increased in size, during the study. Patient 31617-0006 had a left breast ultrasound that revealed multiple cysts without the appearance of malignancy. The investigator did not categorize the breast masses as related to study medication. Two patients were hospitalized during this study. Patient 31618-001 took an intentional overdose of Nyquil and Benadryl on study day 18, for which she was hospitalized and treated. She was withdrawn from the study on day 22. Patient 31622-008 (27 cm^2 treatment group) developed cholecystitis on study day 4. She was hospitalized for 1 day and underwent a laparoscopic cholecystectomy on study day 23. Study medication was stopped only on the day of surgery. Both events were categorized as possibly related to the study treatment by the investigators.

Seven (7) patients were withdrawn from the study because of adverse medical events and all were receiving active treatment. The reasons for withdrawal from the study were: 2 patients withdrew because of application site reactions in the 27 cm^2 treatment group; one patient withdrew because of pain in the right calf plus chest palpitations, and one patient withdrew with an intentional overdose of Nyquil in the 20

cm^2 group; one patient withdrew with depression, one patient withdrew with peripheral edema, bilateral swollen ankles, pain and bilateral calf pain, and one patient withdrew with generalized edema, swelling of hands, feet, face and vagina in the 13.5 cm^2 group.

In sponsor's table 10.4, the incidence of topical irritation was reported. There were no significant differences in skin irritation among treatment groups. In all treatment groups and during all 3 cycles, there was no topical irritation for most observations; between 76.7% and 91.4% of the observations in all groups had "negative" irritation scores. Equivocal reactions were reported for 2.9% to 13.9% of the observations and erythema was reported for 2.9% to 15% of the observations. Of a total of 809 observations, the presence of both erythema and induration was reported in 4 cases (<1%) during the study. Erythema, induration and vesicles were reported in 4 cases, one each in cycles 1 & 2 in the 27 cm^2 group, and 2 cases in cycle 3 in the 13.5 cm^2 group. This was <1% of patients in this study.

As a second measure of patch tolerance, patients evaluated the intensity of itching/pruritis. At each treatment cycle, the patients rated the intensity of pruritis over the previous 28 days. Most patients (68.3% to 90.0%) reported no pruritis during the study. The incidence of pruritis appeared to be related to the size of the patch. Mild pruritis was reported by 7.8% to 10.9% of the 13.5 cm^2 patch users, 18.6% to 22.2% for the 20 cm^2 patch users, and 15.2% to 20.3% of the 27 cm^2 patch users. Moderate pruritis was reported by 0% to 3.1% of the 13.5 cm^2 patch users, 1.4% of the 20 cm^2 patch users, and 4.3% to 15.0% of the 27 cm^2 patch users. Severe pruritis was seen in 4 (1%) of patients during a total of 809 observations. Severe pruritis occurred in cycle one in one patient in the 20 cm^2 group and in 2 patients in the 27 cm^2 group; one additional case of severe pruritis occurred in the 13.5 cm^2 group in cycle 3. There was a significant difference (p=0.0014) among treatment groups during cycle 3. Pairwise comparisons during cycle 3 indicated that the 27 cm^2 patch group was significantly different (p = 0.0014) from each of the three other treatment groups due primarily to the higher incidence of moderate pruritis. For the comparison of E_2 13.5 cm^2 versus 27 cm^2 the p-value was 0.016, for the comparison of E_2 20 cm^2 versus 27 cm^2 the p-value was 0.014, and for the comparison of placebo versus 27 cm^2 the p-value was 0.003.

The sponsor provided summary data on 148 patients who had an endometrial biopsy at baseline and on 123 patients who had a biopsy at the end of cycle 3. At the prestudy visit the placebo group had 4 (10%) of patients with a proliferative endometrium, and 6 (19%), 1 (2%), and 2 (6%) in the 13.5, 20, and 27 cm^2 groups, respectively. At the end of cycle three, the placebo group had 1 (3%) of patients with a proliferative endometrium, and 12 (44%), 19 (54%), and 17 (59%) of patients in the 13.5, 20, and 27 cm^2 groups, respectively. Additionally, one patient was reported to have endometrial hyperplasia and in two patients the diagnosis was made by one of two pathologists. (Per protocol, a patient was considered to have hyperplasia only if the two primary pathologists agreed on the diagnosis.) Patient 31614-0028 was reported by two pathologist to have simple hyperplasia without atypia. She was treated with Provera® and a follow-up biopsy approximately 6 months later was normal. For two patients (31612-0010 and 31618-0027), one of the primary pathologists reported simple hyperplasia without atypia while the other pathologist reported proliferative endometrium or "other". Patient 31612-0010 had received the 20 cm^2 patch. Patient 31618-0027 received a 13.5 cm^2 patch.

In sponsor's table 10.52A, not reproduced, the incidence of bleeding or spotting was reported by week, number of patients and the number of days bleeding/spotting. Seven (7) patients in the placebo group reported bleeding or spotting for a total of 61 days. In the treatment groups, 11, 12, and 10 patients reported a total of 64, 81 and 78 days of bleeding/spotting in the 13.5, 20, and 27 cm^2 groups, respectively. Bleeding in the treatment groups can be inferred to be caused by estrogen stimulation of the endometrium; in the placebo group, bleeding occurred in patients who had proliferative endometrium prior to treatment or return of menses in patients who were amenorrheic for less than one year.

Sponsor's table 10.6.1B reported the percent of patients with laboratory data of potential clinical importance during the study. Although there were a few outliers, most of the abnormal values during therapy were considered by the investigators to be of no clinical importance. One patient had a low hemoglobin and hematocrit after normal prestudy values. This patient, however, reported no vaginal bleeding during the study.

One patient had elevation of her systolic and diastolic blood pressure. Her blood pressure was borderline at prestudy at 158/90 and 134/90. After cycle two and 3, her diastolic pressure ranged between 92 and 98 mm/Hg. One patient also reported weight gain during the study. This weight gain was mild and with a maximum of 1.3 kg for the study.

Adhesion was judged to be good by the investigators in 800 observations at the end of cycles 1, 2, and 3. The patches adhered 90% to 100 % in 93.5% of placebo patients and in 90.5%, 92.5%, 88.3% of patients in the 13.5, 20, and 27 cm^2 groups, respectively. At the end of each cycle, 20 (2.5%) of patients reported that the patch fell off. Others may have fallen off during the other 3 weeks of each cycle. Patch wear was scored by patients as 8 or higher on a scale of 1 to 10. However, there was a significantly (p=0.049) higher incidence of redness at the application site with the active compared to placebo patches. Additionally, there was a significantly (p=0.009) higher incidence of blisters reported with the active patches compared to placebo; pairwise comparisons showed that the only significant difference between groups was the 27 cm^2 treatment group and placebo (p=0.001).

Estradiol (E_2), estrone and estrone sulfate were measured in a total of 395 serum samples collected at baseline and at or near the end of cycle 3. For all three active patch treatment groups, there was a statistically significant increase in E_2 concentrations at cycle 3 compared to baseline. The baseline E_2 concentrations (geometric mean) were 9.3, 8.1, and 6.7 pg/mL for the 13.5, 20, and 27 cm^2 groups respectively. By the end of cycle three, these concentrations increased to 35.0, 39.5, and 41.1 pg/mL for the 13.5, 20, and 27 cm^2 groups, respectively. Additionally, there were no apparent effects of age, race, smoking, or body weights on serum concentrations of E_2.

8.1.5 Reviewer's comments/conclusions of study results:

In this randomized, placebo-controlled study of twelve weeks duration, the 13.5 cm^2, the 20 cm^2 and the 27 cm^2 transdermal patches were statistically significantly better than placebo for the relief of vasomotor symptoms. Efficacy was noted with all treatment patches by the fourth week and was maintained throughout the 12 weeks of treatment. Safety is comparable to other estrogen replacement patches, with the 27 cm^2 III TS patch producing more vaginal bleeding, discontinuations, greater patch pruritis and irritation, and less patch adherence than the smaller two dosages. Patch adherence appeared acceptable from the investigators and patient's prospective with approximately 83.1% to 93.8% of patches adhering 90% to 100% during the fourth week of the treatment cycles.

Study 0802E1-317-US

8.1.1

The primary objective of this study was to compare the efficacy and safety of three different strengths of the 7-day E_2 III TS with those of placebo for the relief of vasomotor symptoms and atrophic vaginitis associated with the menopause. Secondary objectives were to assess the effects of the E_2 III TS on quality of life indicators and to examine population pharmacokinetics of the E_2 III TS. Patch wear evaluations were also conducted. Descriptive data for the Climara TS (another E_2 7-day patch) were also collected in this study.

8.1.2 Design

This was a twelve week, double blind, multiple dose, randomized, placebo controlled, parallel multi-center study with an open-label Climara arm.

8.1.3 Source and number

The study plan called for enrolling 375 patients, with completion of approximately 250 (5-treatment groups of 50 patients each). There were 385 patients enrolled at 28 sites (does not include investigational sites where no patients were enrolled) and 355 patients completed the study.

Inclusion Criteria:

Inclusion criteria are identical to Study 0802E1-316-US

Exclusion Criteria:

Exclusion criteria are identical to Study 082E1-316-US

Patients could be withdrawn from the study if they did not use the patch for intervals longer than 96 continuous hours in any week or a total of 144 discontinuous hours in any consecutive cycles. For patients using the Climara® patch, the same criteria were applied for the 3-week period when the patients wore the Climara patch. If a patient failed to return for the necessary visits, an effort was made to determine the reason for withdrawal. In addition, if a patient withdrew from the study prematurely, the investigator would attempt to retrieve any study materials and repeat the assessments done at screening (e.g., physical and gynecologic examinations, laboratory safety screen). Any patients withdrawn from the study before completion were not replaced.

Study Procedures:

Study procedures were consistent with Study 082E1-316-US; except for use of the active control patch Climara, which is manufactured by Wyeth-Ayerst.

8.1.3.2

Efficacy

The changes from baseline in the average daily number and severity of patient's hot flushes were used as the primary efficacy variable. Each week of treatment was compared with the baseline. One-way analysis of variance (ANOVA) was used to compare the efficacy evaluations among treatment groups. Since the Climara group was not blinded, it was considered inappropriate to include it in the statistical analyses, as if it were a fifth blinded group. Therefore, no pairwise comparisons involving Climara were preformed. However, descriptive statistics and 95% confidence intervals were provided. This approach to the analysis is consistent with the methods described in the protocol. Multiple comparisons of the investigational patches versus placebo were made through a protected least significant difference approach. Also, 95% confidence intervals of the mean changes from baseline for all study groups were provided.

Fisher's exact test was to be used for comparisons among treatment groups of the change in the proportion of vaginal epithelial cells. However, alternate acceptable method of analyzing the vaginal maturation index (VMI) was used consistent with the approval of the estradiol vaginal ring. One-way ANOVA was used for analysis of the mean changes from screening in the proportions of each cell category of the VMI.

Fisher's exact test was used for comparisons between treatment groups of patients who withdrew, both overall and for specific reasons. This test was also used to compare the incidence of skin irritation and other adverse experiences. The pair-T-Test was used to test for significant changes in laboratory data and vital signs over time, with treatment groups. Between group comparisons were made by analyses of covariance (ANCOVA) with baseline values uses as the covariate.

The quality of life questionnaire and Patch Wear Evaluation were analyzed in a similar manner to Study 0802E1-316-US.

Safety

The safety analyses were based on clinical and laboratory reports and reports on skin irritation. All patients who entered the drug administration period were included in the analysis of safety. Mean changes in clinical safety variables (blood pressure, weight, and endometrial biopsy) and laboratory data (chemistry and hematology) are presented in a series of tables, which will be summarized. Any patient demonstrating hyperplasia (based on the agreement of two study pathologists) at the end of he study were given appropriate treatment. Local skin application site reactions were rated by the patient and recorded by the investigator at Visits 4, 5, and 6. The investigator assessed Patch adhesion at Visits 4, 5, and 6.

8.1.3.3

There is large variability within and between patients and differences across study sites were expected because of the subjectivity of hot flush measurements. The plan called for enrolling 375 patients (5 groups of 75 patients each) so that approximately 250 patients (5 treatment groups of 50 patients each) could complete the study. A difference of 16 flushes per week in the mean number of reductions between the active treatment groups and the placebo group was considered clinically meaningful. With approximately 50 patients per treatment group, the study had 90% power to detect such a difference.

8.1.4 Results

There were 385 patients enrolled in this study; 230 received one of the three sizes of E_2 III TS patches, 78 received placebo, and 77 received Climara. Table 5 summarizes the analyzed populations:

Table 5

SUMMARY OF POPULATIONS ANALYZED FOR SAFETY AND EFFICACY, NUMBER OF PATIENTS

Population Subset	E_2 III TS 13.5 cm^2	E_2 III TS 20 cm^2	E_2 III TS 27 cm^2	Placebo	Climara	Total
Safety	72	79	79	78	77	385
Intent-to-treat	71	78	79	78	77	383
Evaluable-for-efficacy	68	66	71	69	62	336

Note: Two patients were excluded from the ITT. One patient (31708-004) in the 13.5 cm^2 group and one patient (31736-008) in the 20 cm^2 group were excluded from the ITT because they received treatment had had baseline flush data, however, no on-therapy flush data were available.

Table 6 (sponsor's table 8.8.2A) summarizes the primary reasons for discontinuation, with number (%) of patients:

TABLE 8.2.2A. PRIMARY REASONS FOR DISCONTINUATION, NUMBER (%) OF PATIENTS

Reason	E_2 III TS 13.5 cm^2 (n = 72)	E_2 III TS 20 cm^2 (n = 79)	E_2 III TS 27 cm^2 (n = 79)	Placebo (n = 78)	Climara (n = 77)	Total (n = 385)
Total	5 (7)	5 (6)	6 (8)	7 (9)	7 (9)	30 (8)
Adverse reaction	2 (3)	2 (3)	4 (5)	2 (3)	1 (1)	11 (3)
Failed to return	1 (1)	2 (3)	2 (3)	0	1 (1)[a]	6 (2)
Other medical event	1 (1)	0	0	1 (1)	0	2 (<1)
Other non-medical event	0	0	0	1 (1)	1 (1)	2 (<1)
Patient/subject request	0	0	0	0	2 (3)	2 (<1)
Protocol violation	0	0	0	2 (3)	0	2 (<1)
Unsatisfactory efficacy response	1 (1)	1 (1)	0	1 (1)	2 (3)	5 (1)

A: The same reason for discontinuation (back strain) for patient 31714-0045 is reported in two different ways in the case report form: as "failed to return, back strain" and as "discontinued for adverse event, accidental injury, back strain."

Thirty patients' (30) or 8% discontinued for any reason. Of that total, the majority discontinued for an adverse reaction or "failed to return."

A total of 27 patients in the five treatment groups had insufficient baseline hot flush data. There were 4 patients in the placebo group, 4 patients in the Climara group, and 3, 10, and 6 in the 13.5, 20, and 27 cm^2 groups, respectively. Additionally, there were 11 patients enrolled in this study who remained in the study despite inclusion criteria violations. Five of 11 had not had a year of amenorrhea and had either estradiol levels too high or FSH levels that were too low to qualify for menopausal status. Other patients allowed to remain in the study despite inclusion criteria violations include one patient with a BMI too high, one patient who smoked greater than 15 cigarettes/day, two patients with increased cholesterol levels, and two patients with increased triglycerides levels.

Comment: twenty-seven (27) patients were allowed to remain in the study despite flush data of < 60/ week. Since the baseline flush mean data ranged from 12.5 to 13.5 between treatment groups, this is not felt to be a major concern.

A total of 70 patients (18.3%) of the ITT population took prohibited medications during the study. Of this total, the largest majority were either chronic antihistamines 26 (37.1%) or 23 (32.8%) who took narcotic analgesics. Of interest were 3 patients who took either Premarin, Estradiol cypionate or DHEA, 8 patients who were taking psychotropic drugs > 2 times per week and one patient on a Belladona derivative.

Comment: The evaluable patient population will not the primary focus of the efficacy evaluation. As in the 316-US study, the ITT population is the primary focus for evaluation. The inclusion of the five patients in the study with estradiol levels too high or FSH levels to low to qualify for menopausal status will not dilute efficacy data by any significant amount due to the size of the study, nor will the inclusion of the 3 patients receiving hormones or related agents.

The sponsor presented baseline demographic information for all patients in table 8.2A. Due to the size of this table, information will be summarized. In general, there were no significant baseline differences between treatment groups. The mean age was approximately 51.7 years of age for all treatment groups. Ethnic origin revealed patients to be 83% White, 9% Black, 6% Hispanic, < 1 % Asian and <1%. Other treatment groups were comparable as to height, with a mean of 163.9 cm, weight with a mean of 67.3 kg;

and Body mass index with a mean of 24.9 kg/m^2. Sixty-two percent of patients underwent a natural menopause and 38 percent had a surgical menopause. Fifty-two percent had no hysterectomy, while 48% had undergone a hysterectomy. The use of alcoholic beverages and cigarette use was also comparable between groups.

Efficacy

The ITT population included all patients randomized to the study who applied at least one patch and had at least 1 day of diary flush data for any week while on treatment. These patients were included in the analysis or the week they participated. Patients who applied a patch but had no diary flush data available for that week were not included in the analysis for that week.

Table 7 shows the analysis of the mean daily number of hot flushes for the ITT population. This table is modified from the sponsor's table 4 and shows weeks 1 through 4 of treatment and weeks 8 and 12 of treatment:

TABLE 7 SUMMARY OF MEAN DAILY NUMBER OF HOT FLUSHES (ITT)

17B-ESTRADIOL PROTOCOL 0802E1-317-US (ITT)

	13.5 cm^2 PATCH	20 cm^2 PATCH	27 cm^2 PATCH	PLACEBO
Cycle 1				
WEEK ONE				
NO. OF PATIENTS	71	78	79	77
BASELINE MEAN (+/-SD)	12.9 +/- 4.4	12.5 +/- 5.2	13.2 +/- 5.1	13.5 +/-5.8
THERAPY MEAN (+/-SD)	8.9 +/- 4.5	8.8 +/- 4.5	8.8 +/- 5.0	9.5 +/-5.9
MEAN CHANGE (+/-SE)	-4.0 +/- 0.5	-3.7 +/- 0.4	-4.4 +/- 0.6	-4.0 +/-0.5
MEAN % CHANGE (+/-SE)	-29.8% +/- 3.9	-28.5% +/- 3.0	-32.0% +/- 3.6	-30.6%+/-3.4
P value	< 0.001***	< 0.001***	< 0.001***	0.001***
WEEK TWO				
NO. OF PATIENTS	71	78	79	76
BASELINE MEAN (+/-SD)	12.9 +/- 4.4	12.5 +/- 5.2	13.2 +/- 5.1	13.5 +/-5.8
THERAPY MEAN (+/-SD)	6.9 +/- 4.4	6.7 +/- 4.4	6.5 +/- 5.3	8.5 +/-5.7
MEAN CHANGE (+/-SE)	-6.0 +/- 0.6	-5.8 +/- 0.5	-6.8 +/- 0.6#	-5.0 +/-0.5
MEAN % CHANGE (+/-SE)	-44.9% +/- 4.0	-45.9% +/- 3.2	-51.0% +/- 3.9	-38.5%+/-3.4
P VALUE	< 0.001***	< 0.001***	< 0.001***	<0.001***
WEEK THREE				
NO. OF PATIENTS	71	78	77	74
BASELINE MEAN (+/-SD)	12.9 +/- 4.4	12.5 +/- 5.2	13.2 +/- 5.1	13.4 +/-5.8
THERAPY MEAN (+/-SD)	5.4 +/- 4.6	5.1 +/- 4.5	5.1 +/- 6.3	7.8 +/-5.7
MEAN CHANGE (+/-SE)	-7.6 +/- 0.7#	-7.5 +/- 0.5#	-8.1 +/- 0.8#	-5.6 +/-0.6
MEAN % CHANGE (+/-SE)	-57.2% +/- 4.3	-60.4% +/- 3.2	-61.7% +/- 4.8	-43.1%+/-3.6
P VALUE	< 0.001***	< 0.001***	< 0.001***	0.001***
WEEK FOUR				
NO. OF PATIENTS	71	77	77	75
BASELINE MEAN (+/-SD)	12.9 +/- 4.4	12.5 +/- 5.2	13.2 +/- 5.1	13.4 +/-5.8
THERAPY MEAN (+/-SD)	4.6 +/- 4.4	4.2 +/- 4.4	3.9 +/- 4.8	6.8 +/-5.5
MEAN CHANGE (+/-SE)	-8.3 +/- 0.7#	-8.3 +/- 0.5#	-9.3 +/- 0.7#	-6.6 +/-0.6
MEAN % CHANGE (+/-SE)	-63.9% +/- 3.9	-67.8% +/- 3.2	-71.0% +/- 3.6	-50.7%+/-3.6
P VALUE	< 0.001***	< 0.001***	< 0.001***	0.001***
WEEK EIGHT (CYCLE 2)				
NO. OF PATIENTS	70	75	75	72
BASELINE MEAN (+/-SD)	12.8 +/- 4.3	12.4 +/- 5.2	13.3 +/- 5.1	13.5 +/-5.9
THERAPY MEAN (+/-SD)	2.7 +/- 3.9	2.3 +/- 3.7	2.0 +/- 3.3	6.1 +/-5.7
MEAN CHANGE (+/-SE)	-10.1 +/- 0.6#	-10.1 +/- 0.6#	-11.3 +/- 0.7#	-7.4 +/-0.7
MEAN % CHANGE (+/-SE)	-78.8% +/- 3.5	-82.5% +/- 2.9	-84.5% +/- 2.8	-56.2%+/-4.0
P VALUE	< 0.001***	< 0.001***	< 0.001***	0.001***
WEEK TWELVE (CYCLE 3)				
NO. OF PATIENTS	66	72	72	69
BASELINE MEAN (+/-SD)	12.9 +/- 4.4	12.5 +/- 5.3	13.1 +/- 4.7	13.4 +/-6.0
THERAPY MEAN (+/-SD)	2.2 +/- 3.4	1.8 +/- 3.5	1.3 +/- 2.8	4.5 +/-4.8
MEAN CHANGE (+/-SE)	-10.6 +/- 0.6	-10.8 +/- 0.7#	-11.7 +/- 0.6#	-8.9 +/-0.7
MEAN % CHANGE (+/-SE)	-82.5% +/- 3.2	-87.2% +/- 2.6	-89.3% +/- 2.4	-67.9%+/-3.5
P VALUE	< 0.001***	< 0.001***	< 0.001***	0.001***

= MEAN SIGNIFICANTLY DIFFERENT FROM PLACEBO USING ONE-WAY ANOVA (EXCLUDING CLIMARA).

P <0.001 level denotes statistically significant difference changes from Baseline (Based on Paired T-Test)

Note that at week 2, the 27 cm^2 E_2 III TS patch was significantly different from placebo; at week three all three patches were significantly different from placebo using a one- way ANOVA analysis. This statistical difference was maintained at weeks 8 and 12. Note the high placebo response rate that exceeds 50% at week four and is maintained throughout the remaining 8 weeks. Although 52 patients were excluded from the efficacy-evaluable analyses, results remain consistent. Additionally. when Climara data is included, is appears that Climara is more comparable to the 27 cm^2 III TS patch in cycle 1; in cycles 2 and 3 the 20 cm^2 and 27 cm^2 III TS patches are very similar to Climara, with very little efficacy difference observed between the 20 cm^2 and 27 cm^2 patches in this study.

The sponsor's table 6 is a summary table of mean daily severity of hot flushes in the ITT population. The severity of each hot flush was recorded as mild (1), moderate (2), or severe (3). The average baseline severity was computed during the 14-day screening period and was calculated using a one-way ANOVA method, which excluded Climara. Due to the length of table 4, and its similarity to table 6, it will be briefly summarized. Beginning in week 3, all 3 treatment groups were statistically different from placebo. For the 13.5 cm^2 patch, however, efficacy was not maintained based on this endpoint for the remaining 8 weeks.

Comment: In the placebo-controlled trial 0802E1-316US, the 20 cm^2 III TS patch was effective when compared to placebo.

As a secondary objective parameter, the sponsor studied the vaginal maturation index. The maturation index is the relative ratio of basal/parabasal cells, intermediate cells, and superficial cells evaluated from vaginal smears taken at baseline and at week 12. The results show that the percentage of superficial cells increased significantly from screening values and the percentage of parabasal cells decreased significantly from screening values in all the active E_2 treatment groups. The mean increases from screening for superficial cells were 11.09%, 15.09%, and 21.11% for the 13.5, 20, and 27 cm^2 treatment groups, respectively. The mean decreases from screening for parabasal cells were 23.00%, 23.93%, and 19.26% for the 13.5, 20, and 27 cm^2 treatment groups, respectively.

The sponsor reported data on two quality-of-life questionnaires, the SF-36 and the WHQ. The analyses of these tables represent patients who completed questionnaires both at baseline and on therapy. In the SF-36 questionnaire, the scores for the first eight subscales range from 0 to 100 and increases in the subscale indicate improvements. However, for the health transition question, the scale ranges from 1 to 5 and a decrease indicates improvement. In the WHQ, the scores ranges from 0 to 1 for each subscale and decrease in the subscale scres indicate improvement. Significant improvements were observed in two SF-36 subscales, vitality and mental health. For various other subscales improvements were noted with various patch dosages, including the Climara patch. In the WHQ, decreases were noted in six of nine subscales—anxiety/fears, memory/concentration, sexual behavior, sleep problems, somatic symptoms, and vasomotor.

Safety

All adverse experiences were recorded. Adverse experiences were classified into a standardized terminology using the COSTART (Coding Symbols for Thesaurus of Adverse Reactions Terms), by body system. All tabulations are of the number of patients reporting a specific event, not the number of events reported, because a patient could report a particular event more than once during the study. Patients who had more than one event in a body system are counted only once in the overall (any) category for that body system.

All patients who took medication are included in the safety analysis. Three hundred eighty-five (385) patients had exposure to at least a single patch; 230 of these patients were exposed to E_2 III TS, 78 patients received placebo and 77 received Climara. In sponsor's table 10.1A assessment to patch exposure was shown. At the end of the twelfth treatment week, 345 patients were enrolled in the study, with 210 receiving E_2 III TS.

Data for adverse experiences were analyzed using the treatment emergent adverse events (TEAEs). TEAEs were events not present at baseline or events present at baseline that worsened during the treatment. Descriptive tables 11, 12, and 13 summarized the incidence, severity and relationship to treatment, and body systems. Overall, in table 10.2.2A 266 (69%) of patients in the five treatment groups reported a systemic adverse event. In the 13.5, 20, 27 cm^2 E_2 III TS treatment groups, 52 (72%), 56 (71%), and 61 (77%) patients, respectively, reported adverse events. In the placebo group 51 (65%) and Climara 46 (60%) patients reported adverse events.

Sponsor's table 10 reported TEAEs of 3% or more by any treatment group. This reviewer will report on TEAEs of 5% or more. The TEAE were grouped by body system. It should be noted that body system totals were not necessarily the sum of the individual study events since a patient could report two or more different study events in the same body system. Table 10 will now be summarized in a descriptive fashion due to the size of this table. **Under Body as a Whole**, headache was the most common adverse event reported. It was reported in 24 (31%) of placebo patients, 18 (23%) of Climara patients, and in 23 (32%), 25 (32%), and 22 (28%) of the 13.5, 20, and 27 cm^2 E_2 III TS respectively. Abdominal pain was reported in 6 (8%) of placebo patients, 3 (4%) of Climara patients, and in 7 (10%), 8 (10%), and 11 (14%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Accidental injury was reported in 5 (6%) placebo patients, 6 (8%) of Climara patients, and in 5 (7%), 3 (4%), and 5 (6%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Back pain was reported in 8 (10%) of placebo patients, 4 (5%) of Climara patients, and in 5 (7%), 7 (11%), and 6 (8%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Flu syndrome was reported in 5 (6%) of placebo patients, 4 (5%) of Climara patients, and in 5 (7%), 5 (6%), and 5 (6%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Infection was reported in 3 (4%) of placebo patients, in 7 (9%) of Climara patients, and in 5 (7%), 9 (11%), and 3 (4%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Pain was reported in 5 (6%) of placebo patients, 7 (9%) of Climara patients, and in 7 (10%), 7 (9%), and 5 (6%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively.

Under Digestive system, nausea was reported in 1 (1%) of placebo patients, in 5 (6%) of Climara patients, and in 6 (8%), 5 (6%), and 6 (8%) of patients in the 13.3, 20, and 27 cm^2 E_2 III TS groups, respectively. **Under Nervous system**, insomnia was reported in 6 (8%) of placebo patients, 3 (4%) of Climara patients, and in 3 (4%), 2 (3%), and 5 (6%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. **Under Respiratory system**, pharyngitis was reported in 9 (12%) of placebo patients, in 3 (4%) of Climara patients, and in 9 (13%), 2 (3%) and 8 (10%) of patients in the 13.5, 20 and 27 cm^2 E_2 III TS groups, respectively. Rhinitis was reported in 4 (5%) of placebo patients, in 1 (1%) of Climara patients, and in 3 (4%), 3 (4%), and 7 ((9%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. **Under Urogenital system**, breast pain was reported in 2 (3%) of placebo patients, 7 (9%) of Climara patients, and 8 (11%), 20 (25%), and 21 (27%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Vaginitis was reported in 5 (6%) of placebo patients, in 0 (0%) of Climara patients, and in 4 (6%), 4 (5%) and 6 (8%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. **Under Skin and Appendages**, application site reactions were reported in 5 (6%) of placebo patients, in 9 (12%) of Climara patients, and in 9 (13%), 8 (10%), and 8 (10%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively.

Comment: TEAEs reported in this study are consistent with TEAEs in study 0802E1-316-US and in other transdermal patch studies. Headache, breast pain (usually increased in increasing estradiol dosages), and application site reactions, and either pharyngitis/or rhinitis were shown to be the most common AEs. The only dose response AE reported in this study was breast pain, and this has been reported in other studies.

There were no deaths reported in this study.

Two patients had a serious adverse event during this study. Patient 31712-0014 (27cm^2 group) had an enlarged uterus at entrance into this study. During the study the uterus was noted to be enlarging rapidly. Hysterectomy was performed three months following the end of this study. The pathology report confirmed uterine leiomyoma. Patient 31717-0017 (27cm^2 group) had an end of study biopsy that revealed endometrial hyperplasia. The investigator prescribed medoxyprogesterone acetate 10 mg for 10 days. A second biopsy 6 weeks later also revealed endometrial hyperplasia. The patient was referred to her primary physician for appropriate treatment.

Comment: Both serious AEs appear to be strongly related to unopposed estrogen replacement therapy and occurred in the 27 cm^2 III TS group.

Two patients were hospitalized during this study. Neither event, however, appears to be study related. Patient 31717-0027 had emergency surgery for intestinal obstruction on day 26 of this study. Patient 31729-0035 suffered a right ankle fracture on day 22 of this study.

Fourteen (14) patients were withdrawn from this study because of an adverse medical event. These include: 3 patients in the 13.5 cm^2 withdrew due to breast pain, vaginal bleeding, and the third patient had multiple body system changes including the Cardiovascular system, the Nervous system and Body as a Whole; 2 patients in the 20 cm^2 group withdrew due to body rash and metrorrhagia; in the 27 cm^2 group 4 patients withdrew due to weight gain, insomnia and alopecia, application site reaction, and skin rash; in the placebo group 3 patients withdrew due to intestinal obstruction, tremor plus an application site reaction, and amnesia, insomnia and emotional lability in one patient; in the Climara group one patient withdrew due to an accidental accident and one patient withdrew due to an application site reaction.

The sponsor's table 10.4A reported observations of topical irritation while wearing various patches. There were not significant differences in skin irritation between treatment groups. In all treatment groups and during all 3 cycles, there was no topical irritation for most observations; between 68.8% to 82.9% of observation in all groups had negative irritation scores. Equivocal reactions were reported in 6.9% to 17.9% of the observation and erythema was reported in 4.0% to 14.9% of observations. Of the total of 1080 observations, the presence of both erythema and induration was reported in 22 observations (2%) during the study. Erythema, induration, and vesicles were reported in 10 (<1%) of observations during the study. Erythema, induration, and vesicles occurred in I patient each in cycle 1 in the 13.5 cm^2 group, the placebo group and the Climara group; in cycle 2 erythema, induration and vesicles occurred in 2 patients in the 13.5 cm^2, in 2 patients in the 20 cm^2 group and in 1 patient in the 27 cm^2 group; in cycle 3 erythema, induration, and vesicles occurred in 2 patients in the 27 cm^2 group.

As a second measure of patch tolerance, patients were evaluated for the intensity of itching/ pruritis over the previous 28 days. Most patients (61.8% to 82.7%) reported no pruritis during the study. In most cases, the incidence of pruritis appeared to be related to the size of the patch. Mild pruritis was reported by 13.9% to 16.4% of the 13.5 cm^2 E_2 III TS users, 14.3% to 19.4% of the 20 cm^2 E_2 III TS users, and 18.7% to 22.2% of the 27 cm E_2 III TS users. Moderate pruritis was reported by 1.5% to 3.0% of the 13.5 cm^2 III TS users, 1.3% to 3.9% of the 20 cm^2 E_2 III TS users, 2.7% to 6.9% of the 27 cm^2 III TS users, to 6.5% of the placebo users, and in 5.8% to 11.8% of the Climara patch users. The incidence of severe skin reactions was low. There was one case of severe pruritis in each of the Climara and 20 cm^2 III TS groups and 2 cases in each of the 13.5 cm^2 E_2 III TS and placebo groups.

Comment: Local skin tolerance appears comparable to Climara.

The sponsor provided summary data on 192 patients (including 41 patients in the Climara group) who had endometrial biopsies. At prestudy biopsy, the placebo group had approximately 5 (6%) of patients with proliferative endometrium. At the end of cycle 3 this figure was 4 (10%). The treatment groups, including the Climara group ranged, from 1 (4%) to 5 (12%). At the end of cycle 3, the incidence of proliferative endometrium increased to 11 (46%), 22 (55%), and 19 (50%) in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively, showing the effect of unopposed estrogen upon the endometrium. One patient (31717-0017) in the 27cm^2 group had a diagnosis of endometrial hyperplasia without atypia. The primary pathologists disagreed as to the final diagnosis in two patients. In each of these cases, a third pathologist reported proliferative endometrium.

Sponsor's table 10.5.2 reported the incidence of bleeding or spotting in patients with a uterus, by week, number of patients and number of days. Six patients in the placebo group reported bleeding or spotting for a total of 15 days; 11 patients in the Climara group reported bleeding or spotting for a total of 89 days. In the E_2 III TS groups, 6, 18, and 21 patients reported bleeding or spotting for a total of 68, 179, and 199 days of bleeding/spotting in the 13.5, 20, and 27 cm^2 groups, respectively. Most of the sustained bleeding/spotting occurred in weeks 7 through 12, which suggest increasing proliferative effects of estradiol on the endometrium.

Comment: The amount of bleeding/ spotting in the 20 and 27 cm^2 groups appears to be somewhat high when compared to the placebo, 13.5 cm^2 group, and the Climara group. However, although bleeding/spotting appears high, this did not correlate with an increased rate of withdrawal from the study.

Sponsor's table 10.6.1B reported the number of patients with laboratory data of potential clinical importance during the study. Although there were a few outliers, such as decreased calcium, sodium, and glucose levels in some of the treatment groups, these changes in laboratory tests were not considered clinically significant.

Sponsor's table 10.7.A reported the vital signs of potential clinical importance in all patients. Three patients in the 13.5 cm E_2 III TS group had a systolic blood pressure go > 160 mm Hg; 25 patients from treatment all groups had a diastolic blood pressure of > 90 mm Hg. These increases were evenly distributed among all treatment groups. Six patients had weight gains of >10%, this ranged from 0.32 to 0.86 kg; there were no differences in the treatment groups and this weight change was not considered to be clinically important.

Adhesion was judged during the observations at the end of each cycle. The adhesiveness of 1022 patches was evaluated. There were no significant differences in adherence among treatment groups, although there was a statistical trend favoring Climara of P=0.068 after 7 days of wear. The patches remained completely attached after 7 days in 54 (71%) of placebo patients and 61 (85%) of Climara patients. Patches remained completely adhered after 7 days in 50 (72%), 61 (81%), and 47 (62%) of patients in the 13.5, 20, and 27 cm^2 E_2 III TS groups, respectively. Patch lifted/wrinkled by ¼ in 21% to 26% of E_2 III TS patches and in 4% of Climara patches. Of interest is that blisters were reported by 4% to 9% of patients in all groups. At the end of cycle 3, 0 (0%) of patients in the 13.5 cm^2 groups had patches fallen off, 1 (1.4%) in the 20 cm^2 group, 6 (8.5%) in the 27 cm^2 group, 1 (1.6%) in the placebo group, and 0 (0%) in the Climara group. (Others may have fallen off during the other 3 weeks of each treatment cycle.)

The sponsor conducted population pharmacokinetic analyses on estradiol (E_2), estrone (E_1) and estrone sulfate. Approximately 572 samples were collected. For all three investigational treatment groups, there was a statistically significant increase in E_2 concentrations compared to baseline at cycle 3. The baseline E_2 concentrations (geometric mean) were 6.0, 6.2, 8.0 and 7.1 pg/mL for the E_2 III TS 13.5, 20, and 27 cm^2, and Climara groups respectively. By the end of cycle 3, these concentrations increased to 33.2, 34.8, 52.0, and 10.4 pg/mL for the E_2 III TS 13.5, 20, and 27 cm^2, and Climara groups, respectively. Additionally, there were no apparent effects of age, race, smoking, or body weight on serum concentrations of E_2.

Comment: The low estradiol levels (10.4 pg/mL) obtained in the Climara samples are inconsistent with Climara's clinical efficacy regarding symptom relief. The sponsor does not comment on this discrepancy.

8.1.5.2 Reviewer's comments/conclusions of study results

In this randomized, placebo-controlled study of twelve weeks duration, the 13.5 cm^2, the 20 cm^2, and the 27 cm^2 E_2 III TS transdermal patches were statistically significantly better than placebo. Efficacy was noted with all patches by the fourth week and was maintained throughout 12 weeks of treatment. Safety is comparable to other estrogen treatment patches, with the highest dose (E_2 III TS 27 cm^2) inducing more vaginal bleeding, breast pain, and pharyngitis than the other treatment groups. Patch adherence appeared acceptable from the investigator's and patient's prospective with approximately 83.1% to 93.9% of patches 90% to 100% adhered during the fourth week of cycle 3, with the placebo and 13.5 cm E_2 III TS patches adhering best.

9. Overview of Efficacy—Comparative results between studies

The sponsor performed two randomized placebo-controlled studies, 0802E1-316US and 0802E1-317US, in overlapping time periods between February 5, 1996 and February 22,1998. The sponsor showed by week 4 of treatment, three dosages of E_2 III TS, 13.5 cm^2, 20 cm^2, and 27 cm^2, a statistically significant improvement in vasomotor symptoms over placebo. This statistically significant difference was maintained over the remaining 8 weeks of treatment in both the number and severity of moderate to severe hot flushes. By the end of the second treatment cycle, the 20 cm^2 III TS patch appeared to be very similar in efficacy to the 27 cm^2 IIITS patch. Both studies reported a high placebo effect of > 42% after week 3 to a high of 53.8% at week 9 in the 0802E1-316US study and 67.9% at week 12 of the 0802E1-317US study. The sponsor showed, in an objective manner by the vaginal Maturation Index, a statistically significant difference from baseline to the end of treatment in the percentage of increasing superficial cells produced and a decreased percentage of parabasal cells produced. The subjective SF-36 and WHQ questionnaires showed some improvement in most subscales measured.

Adhesion, since it may affect efficacy, will be reported in this efficacy section. In a total of 1248 observations at the end of each treatment cycle (reporting the fourth week only patches may have fallen off in the previous 3 treatment weeks and not be reported), 88% to 90% of patches were reported to adhere 90% to 100% of the time. Approximately 2.3% to 3.4% of patches fell off in the fourth treatment week. The placebo patch and the 13.5 cm^2 patch had comparable adherence, while the larger patches adhered in the range of 83.1% to 90.5% in the fourth week.

10 Overview of Safety

The sponsor included 1,430 patients in the integrated summary of safety. Retrieved safety data was classified into a standardized terminology using the COSTART system. The primary safety databases were the Phase 3 studies, 316-US and 317-US (Population A) which includes 670 patients and 116 patients who participated in a US study to assess the skin irritation and sensitization potential for the E_2 III TS (study 108). Safety data from studies 316 and 317 were pooled. In addition, supplemental safety data information was obtained from 484 patients who participated in non-IND safety and efficacy studies conducted by W-AR in Europe and from 160 patients who participated in six pharmacokinetic studies conducted in the US. Two pharmacokinetic studies were conducted by W-AR and four by Cygnus. In all studies, 24 patients received E_2 II TS, 993 received E_2 III TS, 267 received placebo, 262 received Climara, 80 received Estraderm, and 230 received various forms of a progestin.

Deaths

No deaths were reported during this clinical program

Significant/Potential Significant Events

In Population A 16/442 (4%) patients in the E_2 III TS treatments groups withdrew because of an adverse event. In all groups including placebo and Climara groups, 21/670 (3%) withdrew because of an adverse event(s). Application site reactions were the most common safety-related event causing withdrawal in this population; there were 5 reports (<1%). Three patients wearing E_2 III TS 27 cm^2 patches withdrew for this reason and I patient each in the placebo and Climara groups.

Treatment emergent adverse events (TEAEs) were reported in 100 (70%) of patients in the 13.5 cm^2 group, in 109 (72%) of patients in the 20 cm^2 group, in 118 (80%) of patients in the 27 cm^2 group, in 99 (66%) of patients in the placebo group, and in 24 (60%) of patients in the Climara group. Adverse events reported by > 5% in each treatment group include the following: headache 127 (19%), breast pain 90 (13%), application site reactions 76 (11%), pharyngitis 47 (7%), abdominal pain 47 (7%), Back pain 38 (6%), nausea 43 (6%), Flu syndrome 33 (5%), and infection 36 (5%). Endometrial hyperplasia was reported in 1 patient each in the 316 and 317 studies, both patients were taking the 27cm^2 patch.

Overall, 76 (11%) of patients reported application site reactions. Of this total, 9 (12%) were in the Climara group. There appears to be no difference in the percentage of application site reactions between E_2 III TS and the Climara group. As expected, the largest patch 27 cm^2 reported the highest percent of application site reactions, 22 (15%). The majority of these cases were mild and resolved spontaneously. As reported earlier, (1%) discontinued the study due to an application site reaction, with the majority in the 27 cm^2 group.

Laboratory Findings/Vital Signs

Based on laboratory data available in these studies, no laboratory abnormality was directly attributable to E_2 III TS or Climara. Additionally, no clinically important vital sign abnormalities were identified. Abnormalities in all study drug groups occurred inconsistently and generally were not associated with adverse events.

Safety Update

On March 24, 1999 the sponsor submitted a letter stating that all available safety information for E_2 III TS was reported in the original NDA. There are no ongoing preclinical or clinical studies; all studies were completed prior to the time of this NDA submission. Therefore, there is no additional safety information to report.

11 Labeling Review

In general, the proposed label, dated August 5, 1999 corresponds to the Labeling Guidance for Non-Contraceptive Estrogen Drug Products dated April 1999. This label is updated after discussion with DRUDP from the original draft label submitted with the NDA. Recommendations to this updated daft label are as follows:

Under Labeling for Health Care Providers

Box Warning: Under [redacted] This section should be moved to Precautions section, under sections E and F. The second paragraph which refers to the [redacted] should be placed under Section E; the first paragraph which refers to the [redacted] should be placed under Section F.

Under Description: the nominal in vivo delivery should be stated as 0.050, 0.075 and 0.1 mg respectively, rather than by [redacted]

Under Clinical Pharmacology, table 1, the dosage should be expressed in mg/day. The pharmacokinetic reviewer should review if [redacted] are relevant for this table.

Under Clinical Pharmacology, the relevance of table 2 should be reviewed by the pharmacokinetic reviewer. Mean serum concentrations of estradiol appear substantially lower than serum levels at steady state.

Under Clinical Pharmacology, Adhesion, the total number of systems tested was 442 in the placebo-controlled studies. To balance the statement that 88% to 90% of the patches observed adhered 90% to 100%, the [redacted]

Under Clinical Studies, the first sentence is appropriate. The [redacted] should be revised to the following: After four weeks of treatment all three active groups showed a significantly greater reduction in mean daily number and severity of hot flushes vs. placebo.

[redacted] Under Indications, [redacted] should be deleted since this indication was not studied.

Under **Contraindications**, number 1 includes the [redacted] This should be revised to (see Precautions [redacted]

Under **Warnings**, # 1 under endometrial cancer, the second sentence, should read: Most studies show no significant increased risk associated with use of estrogens for less than 1 year [redacted]

Under **Warnings**, #1 under [redacted] this section should be moved to Precautions section under F Pregnancy.

Under **Precautions** have been added. They are Precautions relating to estrogen use and uterine fibroids and patients with metabolic bone disease associated with severe hypocalcemia. This is acceptable.

Under E, Carcinogenesis, Mutagenesis, Impairment of Fertility, the [redacted] referring to congenital defects and DES, should be placed here.

Under F, Pregnancy Category X, the [redacted] relating to use of estrogen in pregnancy and the postpartum period, should be placed in this section.

Under **Adverse Reactions**, first paragraph after table 4, the [redacted]

The next paragraph under **Adverse Reactions**, which begins with [redacted] Although minimally informative, this should be deleted.

Under **Adverse Reactions**, a new # 4 was added. It refers to cardiovascular risks associated with estrogens. Although redundant, it should remain in the label.

Under **Dosage and Administration**, this section should be revised so that the initiation of therapy paragraph appears [redacted] and the use of the TRADENAME system appears [redacted]

Under **Dosage and Administration**, therapeutic regimen, the [redacted] should be revised to the following: TRADENAME may be given continuously [redacted] patients who do not have an intact uterus. In patients with an intact uterus, [redacted] This is especially important in a woman with an intact uterus who is not using concomitant progestin therapy.

Patient Package Insert

Introduction, first paragraph, fourth sentence, beginning with Estradiol, the word ——— should be deleted. Fifth sentence, same paragraph, the word — should be deleted.

Box Warning, ——— should be deleted.

Under How, Where, and When to Apply TRADENAME, —— paragraph, beginning with TRADENAME should not be taken off during normal baths, showers, or swimming. The second sentence referring to ——— should be deleted. In the third sentence, the word —— should be deleted.

Under Uses of Estrogen, ——————————————— should be deleted.

Under Who Should Not Use Estrogens. bullet, reference is made to unusual vaginal bleeding. The second sentence should state "Your health care provider will assess "the cause of the bleeding" rather than

Under Who Should Not Use Estrogens, third —, "If you have had Cancer", the sentence in the ——————————————— should be deleted.

Under Risks of Estrogens, second paragraph, beginning with Using progestin therapy together with estrogen therapy should be changed from to reduces, the higher risk of uterine cancer related to estrogen use.

Under Risks of Estrogens, the ——————————————— should be deleted.

Under Side Effects, reference to "A spotty darkening of the skin, particularly on the face, which may persists when drug is discontinued" should be deleted.

→ May wish to add here that labeling revisions, as per xx/xx/xx/ are acceptable.

12 Conclusions

The sponsor has demonstrated, through two adequate and well-controlled clinical trials, the safety and effectiveness of E_2 III TS (estradiol transdermal delivery system) in reducing vasomotor symptoms associated with the menopause.

13 Recommendations

Approval of E_2 III TS after acceptable labeling revisions (after concurrence from all disciplines once reviews are completed).

Phill H Price, M.D.

July 27, 1999 ~~me~~
August 23, 1999

I concur,
Marc Mann MD
9/10/99

This review is 32 pages with 4 additional pages of clinical investigators.

CC IND/NDA

HFD-103

HFD-580 (NDA/IND)

HFD-580/Price/LRarick/Mmann/wordFiles:20048mor.nda