CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-870

MEDICAL REVIEW(S)

Medical Officer's Summary of NDA 20-870

1. NDA 20-870
M.O. Review #1

Submission Date: August 8, 1997
Review Completed: July 14, 1998

Drug: Estradiol and Norethindrone acetate transdermal system

Generic name: 17 beta estradiol and norethindrone acetate, USP

Proposed Trade Name: Aliatis™ or CombiPatch ™ Transdermal System

Chemical name: Estradiol USP (estra-1,3,5, (10)-triene-3, 17B
17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate

Sponsor: Rhone-Poulenc Rorer Pharmaceutics Inc.
500 Arcoloa Road
Collegeville, Pa 19426-0107

Phamacologic Category: Estrogen/Progestin

Proposed Clinical Indication: Hormonal Replacement Therapy

Dosages and Route of Administration: 50 mcg/day Estradiol(E^2) in combination with either 140[a], 250, or 400mcg/day Norethindrone acetate(NETA) for either continuous wear or sequential wear

NDA Drug Class: 3S

Related Drugs: Approved estradiol transdermal patches are Estraderm, Climara, Vivelle, Menorest and Alora. This will be the first U.S. combination estrogen/progestin patch approved for hormone replacement therapy.

Related Review: Statistical review dated: June 20, 1998
Biopharmaceutics review dated: July 7, 1998

2. Table of Contents

3. Material Reviewed: Volumes: Volumes 1.1, 1.62-1.132

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 tube. With other hormones, such as pituitary hormones and progesterone, they 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 of 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 women.

Orally, administered estradiol is rapidly metabolized by the 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.

However, at doses necessary to relieve menopausal symptoms and prevent bone loss, estrogens can increase the incidence of endometrial hyperplasia and carcinoma. Depending on the dose and duration of therapy , progestins given in either a sequential or continuous regimen have been shown to successfully decrease these adverse endometrial effects while maintaining the beneficial effects of estrogen on vasomotor symptoms and bone.

Aliatis™ was developed as a transdermal E^2/NETA patch to provide a more convenient and consistent method of progestin administration, improving patient compliance and ensuring concomitant administration with estradiol. The E^2/NETA is dispersed uniformly in an adhesive-based matrix.

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, recently approved in late 1994, 1995 and 1996, 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 and norethindrone over the treatment period. Aliatis™ , if approved, will join the oral regimens Prempro™ and Premphase™ as the only approved combination hormonal replacement treatments (HRT) in the US.

6.2 Important information from related INDs:

Studies in the US with this product were conducted under IND by the sponsor Rhone Poulenc Rorer.

6.3 Foreign experience:

There have been no foreign studies to date. All clinical data have been accumulated in the US.

6.4 Human Pharmacology, pharmacokinetics, and pharmacodynamics:

The delivery of estradiol and norethindrone in a transdermal delivery system, as opposed to oral administration, allows the estradiol and norethindrone to reach the circulation without undergoing first pass metabolism to less active metabolites such as estrone, estriol and their conjugates. This permits the use of lower doses of estradiol and norethindrone delivered in a transdermal fashion to achieve the same pharmacological 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. Norethindrone is metabolized to the 5-beta and 3-alpha norethindrone derivative. Most metabolites are excreted as sulphate and glucuronide conjugates in the urine.

The combined estradiol/norethindrone acetate TDS is designed to deliver 0.05 mg/day estradiol and either 0.14 or 0.25 mg/day of norethindrone (given as an acetate) at the constant rate for up to 4 days. Following the application of the patch on intact skin, steady-state serum concentrations of norethindrone delivered as 0.14 mg/day, ranged between 386-617 pg/mL, with an average concentration of 489 pg/mL. Steady-state estradiol concentrations ranged from 45 to 50 pg/mL for up to 4 days.

The sponsor conducted seven pharmacokinetic studies to assess the systemic norethindrone, estradiol and estrone exposure from Aliatis 50/140, 50/250, and 50/400. Four supportive studies (101, 102, 103, and 105) were conducted to determine the final Aliatis formulation for clinical development and three definitive studies (104, 122 and 126) were conducted in healthy postmenopausal women to assess the pharmacokinetics for NET, estrone and estradiol during single and multiple patch applications.

Study 122 demonstrated that placement of Aliatis on the abdomen resulted in approximately 25% to 28% greater rate and extent of estradiol and norethindrone(NET) absorption when compared to buttock's placement.

In study 126, Aliatis was compared to Estragest, and approved transdermal product in Europe. Estragest is a reservoir patch, not a matrix patch such as Aliatis. Aliatis produced and maintained the targeted steady-state NET concentrations over the patch wear period, whereas the NET profiles following Estragest continually increased to peak concentration prior to patch removal. Although these differences produced higher rates (Cmax) of NET exposure following Estragest, the extent (AUC) of exposure to NET was comparable, but

not equivalent, in the two patches. Overall, pharmacokinetic data suggest that Estragest, when compared to Aliatis, provides higher maximum serum NET concentrations than Aliatis and delivers less estradiol.

Study 104 assessed the steady-state pharmacokinetics of estradiol and NET from Aliatis and compared the estradiol bioavailability to Menorest 50. Multiple patch applications (three 3.5 days wear periods) resulted in the delivery of estradiol and NET serum concentration that were maintained at steady state. Slight differences between maximum and minimum serum concentrations resulted in minimal fluctuation in hormonal concentrations at steady-state. For NET, the rate and extent of NET availability from Aliatis ™ 50/140, 50/250 and 50/400 demonstrated dose linearity. Aliatis ™ 50/250 demonstrated equivalent estradiol bioavailability when compared to Menorest 50. The delivery of estradiol from Aliatis 50/140 was slightly less (Cave = 45 pg/mL) than that of Menorest 50 and Aliatis 50/250 (Cave = 50 pg/mL).

Comment: The sponsor submitted comparative data that showed that other approved 50 ug patches release estradiol in the range of 32-57 pg/mL. This would support the sponsor in its claim that the difference of 5 pg/mL in estradiol delivery between Aliatis(50/140) and Menorest 50 would be unlikely to produce clinically significant differences for the indication of VMS.

7 Description of Clinical Data Sources

Clinical studies were conducted in the US under IND The sponsor conducted 4 primary efficacy studies to investigate two primary efficacy endpoints: vasomotor symptoms and estrogen-induced endometrial hyperplasia. Studies 303 (sequential regimen) and 304 (continuous regimen) were designed to evaluate the effectiveness of 50 mcg/day of estradiol on the reduction of VMS for women with at least 8 hot flushes per day of moderate-to-severe intensity compared to placebo. Studies 201 (sequential regimen) and 202 (continuous regimen) evaluated the endometrial protective effect of three NETA doses on the incidence of estrogen induced endometrial hyperplasia during one year, compared to estradiol alone. These 4 studies include a total of 1,717 postmenopausal women with an intact uterus.

8 Clinical Studies:

Study 303 (Sequential Wear HRT regimen)

8.1.1 Objective/rationale

The primary objective of this study was to evaluate the efficacy of continuous 50 mcg/day E_2 administered transdermally with three doses of NETA (140, 250 and 400 mcg/day) in a sequential-wear regimen, compared to placebo alone, in reducing moderate-to-severe postmenopausal vasomotor symptoms. Secondary objectives of this study include evaluation of the effect of continuous E_2 when administered sequentially with three doses of NETA, compared to placebo alone on the following parameters: genital bleeding, lipid profiles, dermal patch tolerance, patch adherence and selected Quality of Life (QOL) indices, serum concentrations of E_2, E_1 estrone sulfate and norethisterone (NET) and laboratory and clinical safety parameters.

8.1.2 Design

This was a multicenter, randomized, double-blind, 3-cycle (12 week) study of four parallel treatment groups. The study consisted of a 4-week, single-blind, placebo run-in period followed by a 3-cycle (12 week) double blind treatment period. Each cycle of the study was designed to be 28 days to correspond to a physiological premenopausal sex hormone cycle.

8.1.3 Source and number

Two hundred-eight patients were originally planned for inclusion in order to have 144 patients (36 per treatment group) complete the study. Each center was asked to screen enough women to ensure that at least 12 women could be randomized.

Inclusion Criteria:

The study inclusion criteria permitted entry of women who:

- were healthy, postmenopausal, and between the ages of 40 and 70 years inclusive, with an intact uterus;
- had no menses for ≥ 1 year with screening E_2 level < 20 pg/mL and follicle stimulating hormone (FSH) level exceeding the reference laboratory lower limit for postmenopausal women (> 40miu/L);
- had moderate to severe vasomotor symptoms (greater than or equal to eight hot flushes per day base on the average number experienced in the final two weeks of the single blind [placebo] run-in period, and the severity of flushes were, on average, moderate or severe with sweating present during the same two week period);
- had a clinically acceptable pelvic examination and PAP smear at study entry;
- had a clinically acceptable mammogram at screening (or performed within eight months prior to first double-blind patch application);
- had the ability and willingness to complete daily diary records and return to the investigational site for scheduled follow-up visits for the duration of the study; and
- were able to fully understand all study procedures and provide informed written consent to study participation.

Exclusion Criteria:

The study exclusion criteria precluded entry of women who:

- underwent a bilateral oophorectomy;
- had known or suspected malignancies or other serious diseases;
- had a diagnosis of past or current breast, uterine, or other estrogen-dependent malignancy;
- used transdermal estrogen preparation for replacement therapy or non-hormonal medications and/or over-the-counter (OTC) preparations for menopausal symptom relief within four weeks of randomization, and/or use oral/intramuscular estrogen or progestin hormone replacement therapy (HRT) preparations (especially conjugated equine estrogens), or reproductive steroids within eight weeks of randomization;
- had a history of significant allergies (especially multiple drug allergies);
- had any active dermatological disease which could modify skin absorption and/or skin tolerance;
- had undiagnosed genital bleeding in the preceding 12 months (patients who had uncomplicated bleeding with ERT and HRT were eligible for entry);
- had a documented history of endometrial hyperplasia;
- had clinically significant fibrocystic breast disease;
- had a history of documented or active coagulopathy, thrombophlebitis, or thromboembolic disorders;
- had uncontrolled hypertension (diastolic blood pressure ≥ 105 mmHg and/or systolic blood pressure ≥ 190 mm Hg);
- had hyperlipidemia (fasting serum cholesterol ≥ 350 mg/dL and /or triglycerides ≥ 300 mg/dL);
- had overt diabetes mellitus requiring insulin therapy (therapy with oral hypoglycemic agents was permitted);
- had clinically significant renal or hepatic abnormalities;
- were morbidly obese (defined as greater than two times the ideal body weight);
- had a history of alcohol or drug abuse in the year preceding study entry;
- were concomitantly using other HRT agents;
- were concomitantly using drugs for menopausal symptoms, ergotamine (or its derivatives), drugs which could mask evaluation of menopausal symptoms, or drugs which interfere with the metabolism of estrogens;
- participated in any investigational drug study within 30 days prior to screening; or
- possessed an inability to comply with the requirements of a daily symptom/bleeding pattern assessment in a scannable diary format.

Patients were withdrawn from the study if:

- a serious drug-related adverse experience occurred;
- a clinically significant laboratory value, verified by repeat analysis, indicated to the Investigator that the patient would be at risk by continued study participation;
- according to the Investigator, it was in the patient's best interest not to continue in the study; or.
- patient consent was withdrawn.

Study Procedures:

Postmenopausal women with a history of moderate -to-severe vasomotor symptoms (VMS) who gave written consent to participate in the study underwent screening evaluations consisting of medical history, physical examination (including gynecological examination), blood and urine sampling, and mammography. Potential study patients were entered into a 4-week, single-blind, placebo run-in period. Patients were dispensed diaries and were required to record daily assessments of VMS, dermal patch tolerance, patch adhesivity, and genital bleeding/spotting.

Based on assessment of diary information from the last two weeks of the single-blind period, eligible women were randomized to double-blind treatment, provided they met all inclusion-exclusion criteria and had $\geq$ 8 hot flashes per day of moderate-to-severe intensity with sweating present. Patients were instructed to apply the patch to the *lower abdomen*, avoiding areas such as the breast, waistline, areas with many skin folds, areas of skin exposed to direct sunlight, and areas of reddened or irritated skin. Prior to patch application, the skin was to be clean and completely dry.

Patients were dispensed a 4-week supply of placebo patches. For the 28-day single-blind, run-in period, patients wore a placebo patch matched in size to the E_2 -50 patch (14.5 cm^2) during the first two weeks , and a placebo patch matched in size to one of the three E_2/NETA combination patches during the second two weeks. E_2/NETA placebo patches (9 cm^2, 16 cm^2, or 26 cm^2) were randomly dispensed as patients entered the single-blind run-in period.

Upon completion of the single-blind period, patients eligible for the study were randomized to receive one of four double-blind patch treatments administered in a sequential-wear regimen. Patients randomized to the placebo group wore an E_2 placebo patch (14.5 cm^2 size) for the first 14 days of each double-blind treatment cycle, and an E_2/NETA placebo patch (either 9 cm^2, 16 cm^2, or 26 cm^2) for the last 14 days of each 28-day double-blind treatment cycle. Patients randomized to each of the active E_2/NETA treatment groups received the E_2 50 active patch (14.5 cm^2) for the first 14 days of each double-blind treatment cycle, and an E_2/NETA active patch (9 cm^2 delivering 50/140, 16 cm^2 delivering 50/250 or 26 cm^2 delivering 50/400 mcg/day) for the last 14 days of each 28-day double-blind study drug for three 28-day cycles.

Patches were changed every 3.5 days throughout each of the 28 day cycles. In the event that a patch "fell off" at an unscheduled patch wear change time, the same kind of patch was applied from the appropriate replacement "spare" patch supply. After replacement, the patch was changed according to the original schedule.

Prior to randomization, screening/run-in diaries were collected and reviewed for patient eligibility, and unused screening/run-in placebo patches were collected. Women with moderate to severe symptoms who had shown acceptable compliance with daily diary completion in the single blind, placebo, run-in period were entered in to the double-blind period. Patients were randomly assigned to one of four possible study treatments groups: E_2/NETA 50/140, 50/250, or 50/400 (mcg/day hormone delivery) combination patch therapy, or placebo. Each investigator was initially assigned 12 consecutive patient allocation numbers corresponding to three blocks of four treatments.

8.1.3.2
Efficacy

All patients who took at least one dose of study drug, and had at least one post-drug efficacy evaluation, were included in the Intent-to-Treat analyses. This population was used to analyze the primary efficacy parameter and all secondary efficacy parameters.

The primary efficacy parameter was the mean change in the number of hot flushes per day from baseline to the last cycle. The baseline value was defined as the mean number of hot flushes per day recorded during the 14-day window that ended with the last non-missing record prior to randomization. Endpoint was defined as the mean number of hot flushes per day during the 14-day window that ended with the last non-missing record during the randomized treatment period. The intensities of hot flushes were graded on a 10-point scale (None=0, mild 1-3, moderate = 4-6 and severe =7-9). Sweating was graded on a 4-point scale (none =0, mild =1, moderate =2 and severe =3).

The change from baseline to endpoint in the mean number of hot flushes per day was also analyzed using an evaluable population, which excluded patients who were protocol violators. The change from baseline to Cycles 1, 2 and 3 in the mean number of hot flushes per day was summarized in both the ITT and evaluable populations. For Cycles 1, 2 and 3, the mean number of hot flushes at each cycle was defined as the mean during the 14 day window of weeks 3 and 4 of the cycle. The change from baseline in the intensity of the hot flushes and the intensity of sweating was analyzed similarly at each cycle and at endpoint for the ITT population.

To assess vasomotor symptoms, the analysis of the change in the number of hot flushes, and intensity of hot flushes and sweating was conducted using an Analysis of Variance (ANOVA) model with main effects of treatment and investigator. Each E_2/NETA treatment group was compared to the placebo group using a one-sided test at the 0.05 significance level. The pair-wise step-down procedure was used to maintain a family-wise error rate of 5% following a recommendation from FDA (dated January 11, 1996) to use a less conservative adjustment than Bonferroni. With this procedure, each of three comparisons was done sequentially, using a 5% significance level. The high dose was tested against placebo, if this was significant then the middle dose was tested. The low dose was tested only if both the middle and the high dose were significantly better than placebo.

Comment: The sponsor submitted appropriate tables using a pair-wise step-down method. The FDA statistician used a step-down two-sided test at the 0.05 significant level.

Safety:
A patient was included in the ITT population if she was randomized into the double-blind period and wore at least one patch. The ITT population was used for the analysis of safety parameters. Other safety parameters included genital bleeding, patch adhesivity, dermal patch tolerance, lipid parameters, laboratory evaluations and QOL evaluations.

8.1.3.3
A sample size of 36 patients per treatment group assured 90% power to detect a difference of 3.5 flushes per day between an E_2/NETA patch treatment group and the placebo group. This assumed a standard deviation (S.D.) of 4.3 hot flushes per day with a one-sided 0.05 significance level, Bonferroni-adjusted for three multiple comparisons. (See previous discussion in Section 8.1.3.2)

8.1.4 Results

There were 220 patients enrolled into the double blind trial at 26 of 33 centers throughout the US. Fifty - three patients were enrolled in the placebo group, 55 were enrolled in the 50/140 group, 59 were enrolled in the 50/250 group and 53 were enrolled in the 50/400 group. Table 1 (from the sponsor) shows the patient disposition in this study:

Table 1

	Placebo	E_2/NETA			Total
		50/140	50/250	50/400	
	N=53	N=55	N=59	N=53	
	n(%)	n(%)	n(%)	n(%)	
Patients Randomized	53(100)	55(100)	50(100)	53(100)	220(100)
Patients Completing Study	52(98)	46(84)	58(98)	52(98)	208(95)
Total Patients Discontinued from Study	1(2)	9 (16)	1(2)	1(2)	12(5)
PRIMARY REASON FOR DISCONTINUATION					
Lost to Follow-up	0.(0)	1(2)	0 (0)	0(0)	1(<1)
Test Drug Ineffective	0.(0)	1(2)	0 (0)	0(0)	1(<1)
Adverse Clinical Experience[1]	0 (0)	5 (9)	1(2)	0 (0)	6(3)
Adverse Laboratory Experience	0 (0)	0(0)	0(0)	0(0)	0(0)
Deviation form Protocol	0(0)	1(2)	0(0)	0(0)	1(<1)
Consent Withdrawn	1(2)	1(2)	0(0)	1(2)	3(1)
Other	0(0)	0(0)	0(0)	0(0)	0(0)

[1]Includes discontinuations due to clinical adverse experiences or application site reactions

A total of 22 (10%) of patients in the ITT population were excluded from efficacy analyses due to major deviations from the protocol after randomization. The most common reason for non-evaluability (14 patients [6%]) was a baseline intensity of hot flushes of less than 3.5 for a minimum of 10 days. Other reasons for non-evaluability include concomitant use of sedatives, antidepressants and tranquilizers (4 patients [2%]) and concomitant use of drugs for the relief of menopausal symptoms (2 patients [1%]). Nine of the 12 patients discontinued from this study were in the 50/140 group. This appears to be an item of chance, with 5 of 9 patients in this 50/140 group discontinuing due to an application site reaction. Of interest, is that no placebo patient withdrew from this study. This suggest a relatively strong placebo effect, even more than the 40% to 50% usually seen in other ERT studies.

The treatment groups were comparable with respect to race, age, weight, height, BMI, years since menopause, prior HRT use, duration of HRT use, tobacco use, alcohol use, estradiol levels, FSH levels mammography results and the average number and intensity of hot flushes per day.

Baseline demographic characteristics showed the majority of patients were Caucasian ($\geq$ 86% in each treatment group). The mean age was 52 to 55 years, on average, and the body mss indexes (kg/m^2) indicated an appropriate weight to height ratio. Few patients were over 65 years of age (4%) in the placebo group, 5% in the 50/140 group and 8% in the 50/400 group. Most patients were non-smokers. There was a higher percentage of patients who smoked in the 50/400 group compared with other groups, this difference was not significant.

Baseline menopausal characteristics, on average showed women in the study be menopausal approximately five years(range 1 to 38 years). The median duration of menopause ranged from 2.7 years to 5.0 years.

The mean serum FSH levels at baseline were characteristic of an untreated menopausal population with mean values ranging from 84 (± 25) mIU/mL in the 50/400 group to 90 (± 34 mIU/mL in the 50/I40. group. Baseline mean serum E_2 levels were appropriately low (approximately 10 pg/mL).

The majority of patients in each group had not used HRT prior to entry in this study(from 58% in the 50/250 group to 66% in the 50/400 group). For those patients who did have prior HRT, the median duration of HRT use was considerably longer in the 50/400 group (68.1 months) than the placebo group (24 months), and the 50/140 (21 months) and 50/250 (21 months) groups.

Baseline mammography was abnormal in 8(15%) in the placebo group and 16 (29%) on the 50/140 group. Only one patient's abnormality at baseline was considered by the investigator to be clinically significant. The abnormal result was not relayed to the investigator until after the patient had been randomized. This patient was discontinued from the study. Several other patients entered the study and were followed with either repeat mammograms or biopsy.

The following table(sponsor's) shows the primary efficacy variable, mean reduction of hot flushes. All p-values are two-tailed step-down multiple comparisons:

Table 2

CYCLE	PLACEBO		E^2/NETA					
			50/140		50/250		50/400	
	N=53		N=55		N=59		N=53	
	n	Mean +S.E.	n	Mean + S.E.	n	Mean +S.E.	n	Mean +S.E.
Cycle 1	53		53	59	59		53	
Baseline		11.58±0.63		11.38±0.82		10.66±0.40		10.40±0.48
Cycle Mean		8.08±0.54		4.38±0.53		4.61±0.42		3.90±0.39
Adjusted Change		-3.90±0.68		-7.38±0.69		-6.53±0.64		-6.96±0.70
p-value		NA		<0.001		<0.001		<0.001
Cycle 2	52		48		58		52	
Baseline		11.64±0.64		11.14±0.83		10.63±0.41		10.45±0.48
Cycle Mean		6.93±0.56		1.75±0.44		2.17±0.33		1.32±0.30
Adjusted Change		-5.03±0.74		-9.78±0.78		-8.87±0.70		-9.56±0.75
p-value		NA		<0.001		<0.001		<0.001
Cycle 3	51		46		58		52	
Baseline		11.30±0.55		11.23±0.86		10.63±0.41		10.45±0.48
Cycle Mean		6.27±0.59		1.48±0.46		1.47±0.27		1.16±0.30
Adjusted Change		-5.32±0.67		-10.27±0.72		-9.48±0.63		-9.71±0.68
p-value		NA		<0.001		<0.001		<0.001
Endpoint	53		54		59		53	
Baseline		11.58±0.63		11.48±0.81		10.66±0.40		10.40±0.48
Cycle Mean		6.28±0.57		2.38±0.56		1.42±0.26		1.13±0.28
Adjusted Change		-5.54±0.73		-9.34±0.72		-9.51±0.68		-9.66±0.74
p-value		NA		<0.001		<0.001		<0.001

Note the statistically significant p-values for all three treatment cycles when compared to placebo. Review of sponsor's table A3.3 (not shown) shows progressive decreases in the mean number of hot flushes for weeks 2 to 3 and continuing to the end of treatment at week 12. This shows the stability of the estradiol in the patch, and not the increasing doses of NETA.

Table 3 (sponsor's table) shows the adjusted treatment means and p-values comparing the three E²/NETA groups with placebo for the reduction in the intensity of hot flushes: All p-values are two-tailed step-down multiple comparison

Table 3

CYCLE	PLACEBO		E²/NETA					
			50/140		50/250		50/400	
	N=53		N=55		N=59		N=53	
	n	Mean +S.E.	n	Mean + S.E.	n	Mean +S.E.	n	Mean +S.E.
Cycle 1	53		53		59		53	
Baseline		5.36±0.19		5.45±0.21		5.51±0.17		5.23±0.20
Cycle Mean		3.78±0.27		2.14±0.27		2.68±0.26		2.16±0.22
Adjusted Change		-1.68±0.32		-3.45±0.32		-2.93±0.30		-3.06±0.32
p-value		NA		<0.001		<0.001		<0.001
Cycle 2	52		48		58		52	
Baseline		5.37±0.20		5.49±0.19		5.51±0.17		5.20±0.20
Cycle Mean		3.29±0.26		0.91±0.21		1.37±0.21		0.80±0.18
Adjusted Change		-2.08±0.29		-4.67±0.31		-4.19±0.28		-4.30±0.30
p-value		NA		<0.001		<0.001		<0.001
Cycle 3	51		46		58		52	
Baseline		5.36±0.20		5.47±0.20		5.51±0.17		5.20±0.20
Cycle Mean		3.18±0.32		0.82±0.22		0.97±0.18		0.56±0.15
Adjusted Change		-2.20±0.30		-4.84±0.32		-4.57±0.28		-4.58±0.30
p-value		NA		<0.001		<0.001		<0.001
Endpoint	53		54		59		53	
Baseline		5.36±0.19		5.50±0.21		5.51±0.17		5.23±0.20
Cycle Mean		3.24±0.32		1.24±0.29		0.92±0.17		0.64±0.17
Adjusted Change		-2.08±0.31		-4.37±0.31		-4.52±0.29		-4.53±0.31
p-value		NA		<0.001		<0.001		<0.001

Intensity of hot flushes were rated on a 10-point scale (0 (none), 1-3 mild, 4-6moderate and 7-9 severe).

Table 3 mirrors table 2 in that p-values are statistically significant even though the hot flush intensity was rated moderate at baseline. Patient's symptoms appear to be relieved both in number and intensity.

The sponsor conducted a similar analysis (Table 12, not shown) with patients in the intensity of sweating. Sweating is a component of the severity of the hot flush. Having previously reviewed intensity, sweating data will be summarized. Patients rated daily sweating intensity on a scale of 0 (none) to 3 (severe). The mean reduction (±S.E.) in sweating showed statistically significant differences from placebo for all three dosages. At endpoint, the adjusted change was −0.70 ±0.13 in the placebo group, −1.53±0.13 in the 50/140 group, −1.67±0.12 in the 50/250 group and −1.75±0.13 in the 50/400 group. All p-values are < p=0.001. These p-values mirror frequency and intensity and are statistically significant.

Safety:

Two hundred twenty patients, (55 in the 50/140 group, 59 in the 50/250 group, 53 in the 50/400 group and 53 in the placebo group) were evaluated for safety. All patients who were randomized to the double blind treatment and wore at least one patch (ITT population) were included in the safety analysis.

Adverse experiences were classified into a standardized terminology using the COSTART Coding Symbols for Thesaurus of Adverse Reactions Terms, Third Edition. Each patient was counted only once in the incidence count for that preferred term.

Systemic adverse experiences were reported at least once in 42 (79%) of placebo patients, 47(85% of patients in the 50/140 group, 53(90%) of patients in the 50/250 group and 44(83%) of patients in the 50/400 group. Overall, 79% of patients in the placebo group reported AEs while 86% of patients in the active group reported AEs. The majority of these AEs were noted to be mild to moderate in severity.

In sponsor's table 22, not reproduced, the incidence of system adverse reactions $\geq$ or > 5% were reported. Symptoms related to the urogenital system were reported in 36% of the patients in the placebo group compared to 63% to 69% of patients in the E_2/NETA groups. There was little evidence to suggest a dose-related(for NETA) increase in the incidence of AEs when data were grouped by body system and examined across these dose groups.

Under urogenital, breast pain was reported in 5(9%) of placebo patients and in 21(38%), 14(24%) and 22(42%) of patients in the 50/140, 50/250 and 50/400 groups respectively; dysmenorrhea was reported in 4(8%) of placebo patients and 15(27%), 16(27%) and 12(23%) in the 50/140, 50/250 and 50/400 groups respectively; menstrual disorders (bleeding) was reported in 1(2%) of placebo patients and 4(7%), 8(14%) and 11(21%) of patients in the 50/140, 50/250 and 50/400 group respectively; vaginitis was reported in 4(8%) of placebo patients and 4(7%), 10(17%) and 0(0%) of patients in the 50/140, 50/250, and 50/44 group. Differences in the urogenital system are not remarkable and are commonly seen in other forms of ERT.

Differences for the following body systems between active groups and placebo were not remarkable. Under body as a whole, headache was seen in 12(23%) of placebo patients, 10(18%), 14(24%) and 8(15%) of patients in the 50/140, 50/250 and 50/400 group respectively; back pain was reported in 3(6%) of placebo patients and 10(18%), 5(8%) and 7(13%) of patients in the 50/140, 50/250 and 50/400 respectively; under Respiratory, pharyngitis was reported in 0(0%) of placebo patients and 1(2%) and 9(15%) of patients in the 50/140 and 50/250 groups respectively, sinusitus was reported in 5(9%) in placebo patients and 2(4%), 7(12%) and 6(11%) of patients in the 50/140, 50/250 and 50/400 group respectively; under Skin and Appendages 7(13%) was reported in the placebo group and 8(15%), 13(22%) and 10(19%) was reported in the 50/150, 50/250 and 50/400 groups respectively; under Metabolic and Nutritional Disorders 1(2%) was seen in the placebo group and 5(9%), 18(31%), and 7(13%) was reported in the 50/140, 50/250 and 50/400 groups respectively; the Cardiovascular, Digestive and Musculoskeletal system were reported at the 5% levels but individual symptoms under these groups did not reach the 5% level.

Comment: In this study, AEs usually attributable to a progestin such as depression, headache, increased breast tenderness and size, increase appetite and weight gain and decreased libido were indistinguishable from previous studies where patients were treated with estradiol alone.

AEs pertinent to a combination patch or any HRT therapy include bleeding/spotting patterns, the incidence of amenorrhea, patch adhesivity and the incidence of skin site reactions. In this sequential wear regimen, the majority of patients (49% to 74%) of patients in the E_2/NETA groups experienced withdrawal bleeding or spotting in Cycles 1 and 2. At Cycle 1, withdrawal bleeding/spotting occurred in 59%, 71%, and 74% of patients in the 50/140, 50/250, and 50/400 groups respectively. In Cycle 2, withdrawal bleeding occurred in 59%, 72%, and 49% of the 50/140, 50/250 and 50/400 groups. In Cycle 3, withdrawal bleeding occurred in 39%, 31%, and 19% of patients in the 50/140, 50/250 and 50/400 groups, respectively. These percentages are lower than in cycle 2 and are incomplete because the study was to be completed at day 84. Bleeding after day 84 is expected. Irregular bleeding and spotting occurred less frequently in the 50/250 group(9% to 14%) compared to the 50/140 group(19% to 22%) and or the 50/400 group(15% to 34%). The E_2/NETA groups reported similar bleeding/spotting episodes per patient(2.1 to 2.2 days), the mean number of bleeding/spotting days(5 to 6 days), and the bleeding/spotting intensity [1.9 to 2.1 (maximum score 4 for heavy bleeding)]. By bleeding episode, 17%, 38%, and 45% of all patients in the 50/140, 50/250 and 50/400 reported irregular bleeding or spotting at least once during the study. In the 50/250 group, there were an average of two episodes of irregular bleeding or spotting per patient. These episodes had a mean length of seven days and a mean intensity of 1.7 out of 4. More than 80% of patients in the

placebo group were amenorrheic at each cycle of the study. Within cycles 1 and 2, 11% to 22% of patients in the E_2/NETA group experienced amenorrhea.

Patch adhesivity was evaluated by the reviewing investigator who assessed adherence and examined patient diary data. In this sequential-wear study, the E_2 only patch worn for the first two week of each cycle was size 14.5 cm^2. The sizes of the three E_2/NETA patches worn during the last 2 week of each cycle were 9 cm^2, 16 cm^2 and 26 cm^2 for the 50/140, 50/250 and 50/ 400 patch, respectively.

Adherence was judged by the investigator to be complete (<90%) in 87% of all evaluations of the 14.5 cm^2 patch and in approximately 90%, 92% and 92% of the 9 cm^2, 16 cm^2, and 26 cm^2 active E_2 NETA patches, respectively. There was incomplete adherence (75% to 90%) in 6%-10% of patients without any trend as to patch size. Of interest, is 13(7%) of the E_2 active patches "fell off", 4(4%) of the 9 cm^2 E_2 /NETA and 1 (1%) of the two larger active patches.

Patient assessment of patch wear was based on unscheduled patch changes and patch loss(whether or not patches "fell off") on a daily basis in the patient diaries. Each of the E_2 /NETA active patches "fell off", on average, less than 1.5% of the days worn in the study. Overall, approximately, 80% of the patients never had an E_2 /NETA patch fall off during the study. Approximately 10% to 15% of patients reported that the patch fell off only 1 or 2 days in the entire study. Of the active groups, a higher incidence of unscheduled patch removals occurred with the E_2 active patch.

The incidence of application site reaction AEs as assessed by the investigators ranged from 4% to 7% for the active patches and from 0% to 10% for the three sizes of placebo patches. The incidence of skin reactions appeared to be unrelated to either patch size or content. The highest incidence of skin reaction AEs of 10% was documented for the patients wearing the smallest (9 cm^2) placebo patch.

Overall, erythema was the most common reported component of an application site reaction, although it was not apparently related to the active ingredients or patch size. No skin AEs were reported to be severe in intensity. Importantly, no patient discontinued treatment due to an AE application site reaction.

Six patients discontinued from the study due to an AE; five of the six patients were in the 50/140 group and one patient was in the 50/250 group. In the 50/140 group one patient was noted to have metrorrhagia, endometrial biopsy revealed complex hyperplasia with focal epithelial atypia; another patient was noted to have disordered proliferative endometrium; one patient complained of increasing breast pain and dysmenorrhea; one patient complained of breast pain, and the fifth patient complained of severe headaches. In the 50/250 group one patient discontinued due to severe dysmenorrhea and severe vaginal hemorrhage.

Important clinical and laboratory evaluations were as follows: there were no clinically meaningful changes in supine blood pressure, heart rate and body weight. On physical examination common findings included uterine enlargement, vaginal bleeding (menses), and breast examination pain/tenderness; five patients had their vaginal or vulvar atrophy resolve; a total of thirty patients had abnormal PAP smears, these were primarily atypical squamous cells of unknown significance(ASCUS) and were not considered to be related to study drug. One patient had a high grade cervical intraepithelial neoplasm(CIN) which was judged to be remotely related to study drug. Laboratory results which were abnormal were primarily related to serum lipids. Thirteen of 25 abnormal values were HDL-cholesterol values greater than 75 mg/dL and the remaining 12 had values which were < 35 mg/dL. A more significant method of presenting HDL data from the sponsor would have been the change from baseline in HDL, rather than change in mean values. Four patients had abnormal (elevated) triglyceride levels; three were in the placebo group and one was in the 50/140 group. Generally, serum chemistries were within normal limits with approximately one patient per group having an elevated/decreased glucose, BUN, total bilirubin, ALT, LDH, and sodium. Several patients were noted to have decreases in FSH, with the greater decreases associated with higher NETA levels.

The sponsor reported data relating to a health-related quality of life (QOL) survey. Overall and current quality of life perceptions of health status, affect balance, cognitive functioning, sexual functioning (arousability and satisfaction), depression, sleep and urinary incontinence were compared to placebo. On average, scores indicated that all groups generally improved on all the above dimensions of health-related QOL from baseline to the end of the trial. Statistical significance, from baseline to the end of the trial, was achieved in affect balance, sexual arousability and sexual satisfaction in various groups. A significant change was not seen in this 3-month study in urogenital atrophy.

8.1.5 Reviewer's comments/conclusions of study results

In this randomized, double-blind, placebo-controlled study all three dosages of sequential E_2/NETA were statistically significantly better than placebo. Starting in the third treatment week and continuing through the 12th week of treatment, both the frequency and severity of VMS were improved. The sponsor also conducted an analysis of the intensity of sweating and it was statistically significantly better than placebo. Safety appears comparable to other 50 mcg estrogen patches. Common AEs such as breast pain, dysmenorrhea, back pain and headache are seen in comparable percentages of patients historically treated with estrogen only products. Under menstrual disorder, there appears to be greater amounts of irregular bleeding and spotting as the dose of NETA is increased. This is not unexpected because the endometrium had already been primed with estrogen. Application site reactions such as skin irritation and rash were noted < 10% patients in this study. Approximately 10-15% of patients reported that their patch "fell off". This appears comparable to reports seen with other similar size transdermal products.

Study 304 (Continuous Wear HRT regimen)

8.1.1 Objectives

The primary objective to this study was to evaluate the efficacy and safety of continuous 50 mcg/day E_2 administered transdermally with three doses of NETA (140, 250 or 400 mcg/day) in a continuous-wear regimen, compared to placebo alone, in reducing moderate to severe postmenopausal vasomotor symptoms. Secondary objectives of this study included evaluation of the effect of combination E_2/NETA patches, compared to placebo, on the following parameters: genital bleeding, lipid profiles, dermal patch tolerance, patch adherence and selected Quality of Life (QOL) indices, serum concentrations of E_2, E_1, estrone sulfate, and norethisterone(NET), and laboratory and clinical safety parameters.

8.1.2 Design

This was a multicenter-center, randomized, double-blind 3-cycle (12 week) study in parallel treatment groups. The study consisted of a 4-week, single-blind placebo run-in period followed by a 3-cycle (12-week) double-blind treatment period. Each cycle of the study was designed to be 28 days to correspond to a physiological premenopausal sex hormonal cycle.

8.1.3 Source and number

Two hundred-eight patients were originally planned for inclusion in order to have 144 (36 per treatment group) complete the study. Each center was asked to screen enough women to ensure that at least 12 women could be randomized.

Inclusion Criteria:

Identical to Study 303

Exclusion Criteria:

Identical to Study 303

Study Procedures:

Are identical to Study 303 with the exception that the patients wore a placebo patch matched to one of the three E_2/NETA combination patches. Subjects wore either E_2/NETA placebo patches (9 cm^2, 16 cm^2 or 26 cm^2) or matching E_2/NETA delivering 50/140, 50/250 or 50/400 mcg/day of active estradiol and norethindrone acetate for 3 cycles of 28 continuous days.

8.1.3.2

Efficacy and Safety are identical to Study 303

8.1.3.3

Sample size is identical to Study 303

8.1.4 Results

There were 226 patients enrolled into this double-blind trial at 28 of 32 centers throughout the US. Fifty-four patients were enrolled into the placebo group, 58 patients were enrolled into the 50/140 group, 53 patients were enrolled into the 50/250 group and 61 patients were enrolled into the 50/400 group. Table 4 (from the sponsor) shows patient disposition in this study:

Table 4

	Placebo	E_2/NETA			Total
		50/140	50/250	50/400	
	N = 54	N = 58	N = 53	N = 61	n = 226
	n (%)	n (%)	n(%)	n (%)	
Patients Randomized	54(100)	58(100)	53(100)	61(100)	226(100)
Patients Completing Study	47(87)	52(90)	49(92)	55(90)	203(90)
Total Patients Discontinued from Study	7(13)	6(10)	4(8)	6(10)	23(10)
PRIMARY REASON FOR DISCONTINUATION					
Lost to Follow-up	1(2)	0(0)	1(2)	0(0)	2(1)
Test Drug Ineffective	2(4)	0(0)	2(4)	2(3)	6(3)
Adverse Clinical Experience[1]	2(4)	3(5)	1(2)	2(3)	8(4)
Adverse Laboratory Experience	0(0)	0(0)	0(0)	0(0)	0(0)
Deviation from Protocol	1(2)	1(2)	0(0)	1(2)	3(1)
Consent Withdrawn	1(2)	2(3)	0(0)	0(0)	3(1)
Other	0(0)	0(0)	0(0)	1(2)	1<1)

[1]Includes discontinuations due to clinical adverse experiences or application site reactions

A total of 27(12%) of patients in the ITT population were excluded from the efficacy analyses due to major deviations from the protocol. The most common reason for non-evaluability (7 patients [3%]) was concomitant use of sedatives, antidepressants or tranquilizers. Other reasons for deeming patients non-evaluable included patch-wear non-compliance at endpoint (5 patients [2%]) and baseline sweating not

present for a minimum of ten days of record (4 patients [2%]). As in study 303, a good placebo effect is shown, with only 2 patients discontinuing because of an ineffective drug.

Treatment groups were comparable with respect to race, age, weight, height, BMI, years since menopause, prior HRT use, duration of prior HRT use, alcohol use, estradiol levels, FSH levels and mammography results. For the ITT population, there were treatment group differences in the mean number of hot flushes per day of approximately 1.5 between the highest and lowest group. (see Table 5).

Baseline demographic characteristics showed the majority of patients were Caucasian (>83% in each treatment group). The mean age was 52 to 53 years of age with a broad range of ages from 40 to 70 years. Five patients were over 65 years of age. The BMI values indicated a clinically acceptable weight to height ratio(26.09 kg/m^2 to 27.61 kg/m^2) which was similar among treatment group. Most patients were non-smokers(67% to 83%). Baseline menopausal characteristics, on average showed women in the study to be menopausal approximately 5 years(range 1 to 23 years). The median duration of menopause ranged from 3 to 3.5 years.

The mean serum FSH levels at baseline were characteristic of an untreated menopausal population with mean values (±S.D.) ranging from 88 (±26) mIU/mL in the 50/400 group to 91 (±29) mIU/mL in the 50/250 group. Baseline mean serum E_2 levels were appropriately low (approximately 10 pg/mL or less).

Approximately one-half of the patients in each group used HRT prior to entry in this study. The median duration of prior HRT use was longer in the three E_2/NETA groups (24 months -50/140 group, 27 months-50/250 group and 17 months-50/400 group) than the placebo group (10 months).

All patients underwent a mammogram at the initial assessment or within 8 months before the start of the double-blind period. Although abnormalities were noted in 14% to 21% of patients in any group, none were considered to be clinically significant by the investigators. Several patients had repeat mammograms or additional clinical or laboratory evaluations (i.e. biopsies or ultrasounds); results showed the abnormalities to be clinically acceptable and patients were permitted to participate in the study.

Compliance with treatment was defined as the patient wearing a patch for 21 or more of the 28 days per cycle. Patients in the double-blind portion of the study were noted to be complaint from 94% to100% of treatment cycles.

The following table (sponsor's) shows the primary efficacy variable, mean reduction of hot flushes. All p-values as two-tailed step-down multiple comparisons:

Table 5

	PLACEBO CYCLE		E²/NETA 50/140 N=58		E²/NETA 50/250 N=53		E²/NETA 50/400 N=61	
	n	Mean +S.E.	n	Mean + S.E.	n	Mean +S.E.	n	Mean +S.E.
Cycle 1	51		56		50		61	
Baseline		10.56±0.56		11.21±0.49		10.28±0.37		9.81±0,29
Cycle Mean		6.65±0.72		5.20±0.66		3.07±0.55		3.20±0.55
Adjusted Change		-4.43±0.63		-6.40±0.60		-7.64±0.62		-7.06±0.58
p-value		NA		0.014		<0.001		<0.001
Cycle 2	50		54		49		58	
Baseline		10.61±0.57		11.11±0.48		10.16±0.36		9.81±0.29
Cycle Mean		5.29±0.63		3.03±0.66		1.55±0.40		1.81±0.50
Adjusted Change		-5.77±0.57		-8.53±0.55		-8.94±0.56		-8.51±0.53
p-value		NA		<0.001		<0.001		<0.001
Cycle 3	47		51		49		55	
Baseline		10.42±0.51		11.15±0.50		10.16±0.30		9.84±0.29
Cycle Mean		4.93±0.69		2.13±0.58		1.12±0.33		0.61±0.20
Adjusted Change		-5.83±0.51		-9.46±0.49		-9.22±0.49		-9.65±0.48
p-value		NA		<0.001		,0.001		<0.001
Endpoint	51		57		52		61	
Baseline		10.56±0.56		11.45±0.53		10.37±0.38		9.81±0.29
Cycle Mean		4.80±0.66		2.63±0.65		1.78±0.52		1.33±0.43
Adjusted Change		-6.20±0.58		-9.29±0.56		-8.86±0.57		-8.98±0.54
p-value		NA		<0.001		<0.001		<0.001

Note the highly statistically significant p-values for all three treatment cycles when compared to placebo. In this study the sponsor did not generate a table showing week-by-week comparisons for the 12 weeks of treatment.

Table 6 (sponsor's) shows in the ITT population the adjusted treatment means and p-values comparing the three E_2/NETA groups with placebo in the reduction in the intensity of hot flushes: All values are two-tailed step-down multiple comparisons.

Table 6

	PLACEBO CYCLE N=54		E^2/NETA 50/140 N=58		E^2/NETA 50/250 N=53		E^2/NETA 50/400 N=61	
	n	Mean +S.E.	n	Mean + S.E.	n	Mean +S.E.	n	Mean +S.E.
Cycle 1	51		55		49		61	
Baseline		5.49±0.17		6.00±0.22		5.95±0.22		5.59±0.17
Cycle Mean		3.36±0.32		2.88±0.35		1.75±0.30		1.86±0.29
Adjusted Change		-2.30±0.34		-3.22±0.33		-4.33±0.34		-3.84±0.32
p-value		NA		0.036		<0.001		<0.001
Cycle 2	50		53		49		58	
Baseline		5.50±0.17		5.99±0.23		5.87±0.21		5.60±0.17
Cycle Mean		3.06±0.33		1.72±0.32		0.89±0.23		1.04±0.26
Adjusted Change		-2.45±0.34		-4.32±0.33		-5.08±0.33		-4.56±0.32
p-value		NA		<0.001		<0.001		<0.001
Cycle 3	46		50		49		55	
Baseline		5.58±0.18		6.08±0.23		5.87±0.21		5.58±0.16
Cycle Mean		2.76±0.35		1.26±0.30		0.72±0.21		0.38±0.12
Adjusted Change		-2.60±0.32		-4.78±0.31		-5.11±0.30		-5.13±0.29
p-value		NA		<0.001		<0.001		<0.001
Endpoint	50		56		52		61	
Baseline		5.48±0.17		6.02±0.22		5.98±0.21		5.59±0.17
Cycle Mean		2.63±0.33		1.44±0.31		1.03±0.27		0.79±0.24
Adjusted Change		-2.79±0.35		-4.58±0.33		-4.96±0.34		-4.79±0.32
p-value		NA		<0.001		<0.001		<0.001

Intensity of hot flushes were rated on a 10-point scale (0 (none), 1-3 mild, 4-6 moderate and 7-9 severe). Table 6 mirrors table 5 in that p-values are statistically significant even though the hot flush intensity was rated moderate at baseline. Patient's symptoms appear to be relieved both in number and intensity.

The sponsor conducted a similar analysis (table 12, not shown) with patients relating to the intensity of sweating. Sweating is a component of the severity of hot flushes. Having reviewed the intensity of the hot flush, sweating will be summarized. Patients rated daily sweating intensity on a scale of 0 (none) to 3 (severe). The mean reduction (S.E.) in sweating showed statistically significant differences from placebo for all three dosages. At endpoint, the adjusted change was -0.88±0.14 for placebo, -1.65±0.13 in the 50/140 group, -1.70±0.13 in the 50/250 group and -1.65±0.13 in the 50/400 group. All p-values are at the <0.001 level except for the 50/140 group in cycle 1, were p= 0.035. These p-values mirror those of frequency and intensity.

Safety:

Two hundred twenty-six patients (58 in the 50/140 group, 53 in the 50/250 group, 61 in the 50/400 and 54 in the placebo group) were evaluated for safety. All patients who were randomized to the double-blind treatment and wore at least one patch (ITT population) were included in the safety analyses.

Adverse experiences were classified into a standardized terminology using the COSTART Coding Symbols for Thesaurus of Adverse Reactions Terms, Third Edition. Each patient was counted only once in the incidence count for that preferred term.

Systemic adverse experiences were reported at least once in 36(67%) of placebo patients, 44(76%) in the 50/140 group, 43(81%) in the 50/250 group and 52(85%) of patients in the 50/400 group. Overall, 67% of patients in the placebo group reported AEs while 81% of patients in the three active groups reported AEs. The majority of these AEs were noted to be mild in severity.

In sponsor's table 22, not reproduced, the incidence of systemic adverse reactions equal to or > 5% were reported. Symptoms related the urogenital system were reported in 20% of placebo patients and 40% to 60% of patients in the E_2/NETA groups. There was little evidence to suggest a dose-related (for NETA) increase in AEs when data were grouped by body system and examined across dose groups except for breast pain, dysmenorrhea, and back pain. Breast pain was reported in 11(20%) of placebo patients, and in 23(40%), 33(62%) and 42(69%) of patients in the 50/140, 50/250, and 50/400 groups, respectively; dysmenorrhea was reported in 1(2%) of placebo patients and 8(14%), 8(15%) and 15(25%) of patients in the 50/140, 50/250, and 50/400 groups, respectively; menstrual disorders were reported in 1(2%) of placebo patients and 3(5%), 5 (9%), and 5 (8%) of patients in the 50/140, 50/250, and 50/400 groups respectively; vaginitis was reported in 1(2%) of placebo patients and 3(5%), 4(8%) and 6(10%) of the 50/140, 50/250 and 50/400 groups, respectively.

Differences in the following body systems between active drug and placebo were not remarkable. Under body as a whole, headache was seen in 9(17%) of placebo patients and 10(17%), 8(15%), and 7(11%) of patients in the 50/140, 50/250, and 50/400 groups respectively; back pain was seen in 2(4%) of placebo patients and 2(3%), 5(9%), and 8(13%) of patients in the 50/140, 50/250, and 50/400 groups respectively; pain was seen in 4(7%) of placebo patients and 6(10%), 1(2%) and 6(10%) of patients in the 50/140, 50/250 and 50/400 groups respectively; depression was seen in 6(11%) of placebo patients and 1(2%), 3(6%), and 2(3%) of the 50/140, 50/250 and 50/400 patients respectively; other body systems such as the musculoskeletal, respiratory and digestive had individual symptoms >5% but these symptoms did not appear to be drug related. Body systems such as the cardiovascular, hemic, lymphatic and special senses had AEs occur at the <5% range.

Comment: The addition of a progestin to estradiol in continuous mode of delivery did not appear to increase common AEs usually associated with the progestin component in other HRT studies such as breast tenderness, headaches, increase appetite and weight gain, and depression.

AEs most pertinent to a combination patch or any HRT therapy is bleeding/spotting pattern, patch adhesivity, and the incidence of skin reactions. Amenorrhea was common with long term administration of a continuous-wear combined estrogen and progestin regimen. With this regimen, all patients who are not amenorrheic are, by definition, considered as having irregular bleeding or spotting. Due to the short, 3-cycle duration of this study, it is not expected that patients would establish a consistent bleeding pattern or become totally amenorrheic. Nevertheless, results are presented in terms of percentage of patients who were amenorrheic.

The percentage of ITT patients in the three E_2/NETA groups were amenorrheic over the entire duration of Cycles 1, 2, and 3 were 37%, 29%, and 20% in the 50/140, 50/250 and 50/400 groups, respectively. When data are summarized as to years since menopause, a higher percentage o women in the three E_2/NETA groups were amenorrheic if they were 55 to 65 years of age (33% to 50%) versus less than 55 years of age (10% to 38%). Similarly, a higher percentage of women were amenorrheic if they were greater than three years postmenopausal (25% to 50%) versus one to three years postmenopausal (17% to 25%).

The percentage of patients who were amenorrheic at cycle 3 decreased as the E_2NETA dose increased, compared to 90% of patients in the E_2 group. In the E_2/NETA groups the percentage of patients who were amenorrheic at cycle 3 ranged from 31% in the 50/400 group to 52% in the 50/140 group. When examined across the entire study, 60% to 75% of all patients in the E_2/NETA groups reported irregular bleeding or spotting at least once during the study. A mean number of 3.3 to 3.3 episodes of irregular bleeding/spotting was reported per patient in the three E_2/NETA groups. The mean length of irregular bleeding/spotting episodes ranged from 6 days in the 50/140 group to 9.1 days in the 50/400 group.

Patch adhesivity was evaluated by the reviewing investigator and patient assessed diary data. In the continuous-wear study the sizes of the three patches were 9 cm^2, 16 cm^2, and 26 cm^2. Patients in the placebo group wore placebo patches matched in size to one of the three E_2/NETA patches listed above. Adherence was considered to be "complete" (>90% adherence) in 89% to 95% of all evaluations. There was incomplete adherence (75% to 90%) in 4% to 5% of patients. For the subset category summaries by age, race, and years since menopause, the results of the investigator assessments of patch adherence were similar to those seen in the ITT population, with the exception of the black subset of patients. In this subset, "complete" patch adherence was noted in a fewer number of evaluations (67% to 80%) of the E_2/NETA group active patches than the ITT population. The difference in the black subset is probably related to the small number of patients treated.

Patients recorded patch changes and patch loss (whether or not patches "fell off") on a daily basis in the patient diaries. Each of the E_2/NETA active patches "feel off" on average less than one percent of the days worn in the study. Overall, in this study, more than 70% of the patients reported that their E_2/NETA patches never "fell off", and 13% to 29% of patients reported that their E_2/NETA active patches "fell off" on one or two days.

The incidence of application site reaction AEs as assessed by the investigators ranged from 0% to 8% for the active patches and from 0% to 6% for the three placebo patches. For any type patch, 92% or more of patients experienced no application site reaction AEs. None of the patients wearing the 9 cm^2 active patch reported any application site reaction and only a few patients in the 16 cm^2 or 26 cm^2 patches had application site AEs.

Overall, erythema was the application site reaction component reported by the largest number of patients (two patients(4%) in the 16 cm^2 active group and four patients(7%) in the 26 cm^2 active group, respectively). One patient in the 16 cm^2 active group experienced severe erythema. The remainder of application site reactions were considered by the investigator to be mild or moderate in severity. No patient discontinued due to an AE application site reaction.

Eight patients discontinued from the study due to an AE; two were in the placebo group (patient due to depression and patient due to increased mood swings[emotional lability]) ; three patients discontinued in the 50/140 group (one due to severe dysmenorrhea, headache and bloating, one due to breast pain and one due to mood swings); one patient discontinued in the 50/250 group due to dysmenorrhea; and two patients discontinued in the 50/400 group due to depression, acne, and insomnia. Important clinical and laboratory values are as follows. Vital sign measurements, which included supine blood pressure and heart rate, and body weight, revealed no clinically meaningful changes from baseline to week 12. On physical examination, the most common findings were suspicious PAP smears, breast pain, an dysmenorrhea. A total of 29(17%) of patients in the active group combined had abnormal PAP smears at endpoint, as compared to 11(22%) patients in the placebo group. Most of these abnormal PAP smears were epithelial cell abnormalities, and are probably not related to study drug. No dysplasia or malignancy was observed at baseline or the end of the study.

Laboratory abnormalities were noted for HDL-cholesterol, where 7 of 26 abnormal values were greater than 75 mg/dl, and the remaining 19 values were < 35 mg/dl. The sponsor did not express the more clinically meaningful change from baseline in HDL. Four patients had total cholesterol of > 300mg/dL but not patient had an LDL cholesterol value which was markedly abnormal. Six patients had markedly abnormal hematology results, two were in the placebo group, while four were in the 50/400 group. Only one hematology value was related to a low hematocrit. There were 9 abnormal serum chemistries reported, none of these values appear to be related to study drug and are clinically significant. As expected, FSH levels were noted to decrease below the 40 mIU/mL level.

The sponsor conducted a QOL survey which assessed the following dimensions: overall and current quality of life, the participants perceptions of their general health status, affect balance, cognitive functioning, sexual functioning (arousability and satisfaction), depression, sleep, and urinary incontinence. On average, scores indicated that all groups generally improved on all the above dimensions of health-relate QOL from baseline to the end of the trial when compared to placebo. Differing groups were able to achieve statistical significance in cognitive function, sexual arousability, and sleep. Significant effects upon vaginal atrophy were not achieved in this 3-cycle study.

8.1.5 Reviewer's comments/conclusion of study results

In this randomized, double-blind, placebo-controlled study all three dosages of continuous E_2/NETA were statistically significantly better than placebo. Starting in the third treatment week and continuing through the 12th week of treatment, both the frequency and severity of VMS were improved when compared to placebo. The sponsor also conducted an analysis of the intensity of sweating and it was statistically significantly better than placebo. Safety appears comparable to other 50 mcg estrogen patches. Common AEs such as breast pain, dysmenorrhea, back pain, and headache are seen in comparable percentages as historically noted in patients on estrogen alone therapy. Menstrual bleeding with this product will range from 39% to 69% in the first three cycles, but bleeding/spotting was not unusually heavy and was not unexpected. Generally, in patients treated with continuous oral HRT, improvement in bleeding or achievement of amenorrhea is not seen until 4-6 months after initiation of treatment. However, these percentages of bleeding/spotting appear high and may become a compliance issue if resolution is not noted over longer periods of use. Application site reactions such as skin irritation were reported as < 8% for all cycles in this study. Approximately 13% to 29% of the patients reported that their E_2/NETA patch "fell off" on one or two days of the treatment cycle. This "fall off" rate appears comparable to reports seen with other similar size transdermal patches.

Study 201 (Endometrial Protection)

8.1.1 Objective/rationale

The primary objective of this study was to evaluate the effect of three dose levels of NETA (140, 250, and 400 mcg) when administered sequentially with continuous estradiol (50 mcg/day) on the incidence of estrogen induced endometrial hyperplasia. Secondary objectives of this study included the evaluation of the effect of three dose levels of NETA administered sequentially with continuous estradiol (50 mcg/day), compared to estradiol alone (50 mcg/day), on the following parameters: VMS, if present at baseline, bone biochemical markers, genital bleeding, patch adherence, dermal patch tolerance, lipid profiles, laboratory an clinical safety parameters, selected parameters of glucose metabolism and coagulation, serum concentrations of estradiol, estrone, and norethisterone, and selected QOL indices.

8.1.2 Design

This was a multicenter, randomized, double-blind, estrogen-only arm controlled, 13-cycle (52-week) study in four parallel treatments groups. The study consisted of an eight week screening period followed by a 13-cycle (52-week) double-blind treatment period. Each cycle of the study was designed to be 28 days to correspond to a physiological premenopausal sex hormone cycle. The four treatment groups will be delineated later.

8.1.3 Source and number

Six-hundred forty-six patients were enrolled at 35 centers throughout the US. Two centers did not enroll any patients. The number of patients enrolled at any one center ranged from six to 36 patients. Most sites (20 of 33) enrolled approximately 20(±4) patients each. In anticipation of as many as 33% of enrolled patients prematurely terminating from the study, 600 patients were originally planned for inclusion in order to have 400 patients (100 per treatment group) complete the study.

Inclusion Criteria:

Were identical with studies 303 and 304 with the exception that eight moderate to severe hot flushes were not required.

Exclusion Criteria:

Were identical to Studies 303 and 304 with the exception of:

- a documented history of endometrial hyperplasia has been replaced with "had a diagnosis of past or current endometrial hyperplasia on biopsy (study entry and treatment based on reading from primary pathologist);
- cervical stenosis or any cervical distortion which would preclude endometrial biopsy.

Patients were withdrawn from the study if:

See Studies 303 and 304. In addition, patients could also be withdrawn for the following:

- on study development of biopsy-proven endometrial hyperplasia occurred;
- they received concurrent chronic (longer than 10-day duration over the entire study period) systemic glucocorticoid therapy.

Study Procedures:

Healthy, postmenopausal women with an intact uterus who gave written consent to participate in the study underwent initial screening evaluations consisting of: medical history, physical examination (including gynecological examination), blood and urine sampling, instruction in daily diary recording and instructions in recording the number of cigarettes smoked, and amount of alcohol ingested during the five days prior to the baseline visit. Women who appeared to qualify for the study based on the initial screening procedures also had a mammogram (if none were done within six months of first patch application), transvaginal sonogram (TVS), and an endometrial biopsy.

All women were instructed in completion of the screening daily diaries. The diary assessed the presence, number, and severity of hot flushes, the presence and intensity of sweating, and the presence and severity of vaginal bleeding. The patients were expected to respond to all of the questions daily and were required to bring the diaries to the baseline visit for review. Any woman who was found unable to complete the diary was excluded from study participation. As a minimum, patients were to report a full two-week diary record prior to the start of double-blind therapy.

Patients who met the inclusion/exclusion criteria and who showed acceptable compliance with completion of daily diaries were randomized to double-blind treatment. Patients were required to maintain daily diaries for the 52 weeks of the study, recording patch wear, daily assessments of VMS, genital bleeding/spotting, dermal patch tolerance, and patch adhesivity. Periodically, patients were also required to complete QOL and food questionnaires and undergo pharmacokinetic (PK) and safety blood/urine sampling.

Upon completion of the single-blind period, patients eligible for the study were randomized to receive one of four double-blind patch treatments administered in a sequential-wear regimen. The four treatment groups were identical to Study 303 with all patches worn on the right or left side of the abdomen.

Patches were changed every 3.5 days throughout each of the 14 28-day cycles. In the event that a patch "fell off" at an unscheduled patch wear change time, the same kind of patch was applied from the appropriate replacement "spare" patch supply. After replacement, the patch resumed changing according to the original schedule.

8.1.3.2

Efficacy

All patients were required to undergo an endometrial biopsy at both screening and at the final visit (or early termination). Although the presence of symptoms at baseline was not mandatory, all patients were required to record daily postmenopausal symptoms(number and intensity of hot flushes and presence and intensity of sweating) onto diaries. Biochemical markers of bone resorption and formation were assessed at baseline, week 24 and week 52.

The primary efficacy parameter was the assessment of the presence or absence of endometrial hyperplasia as determined by two out of three pathologists (blinded to study drug assignment). Biopsies were to be performed at screening and Week 52. An endometrial biopsy was recommended at week 24 if the patient had a TVS measurement greater than 8 mm or experienced excessive bleeding. Additionally, endometrial biopsies were to be performed at the discretion of the investigator based on adverse events and bleeding patterns.

If the patient terminated early, a final endometrial biopsy was not required if one had been performed in the cycle prior to the patient's termination. Also, participation for less than three months did not mandate a final endometrial biopsy.

The baseline biopsy was to be performed during the last week of the four week washout period for transdermal HRT or during the last two weeks of the eight week washout period for oral HRT.

At least two attempts were required to obtain an adequate sample of endometrial tissue at both baseline and end of the study. At baseline, if despite the second biopsy attempt, there was insufficient tissue for histologic evaluation, the result of the TVS was be reviewed. Women with an endometrial thickness of < 5mm were allowed to enter the study.

In order to diagnose hyperplasia, concurrence on the presence or absence of hyperplasia was required from two out of three expert gynecologic pathologists, with all tissue review occurring independently, and with complete blinding as to treatment.

Patients who developed histologic evidence of endometrial hyperplasia during the study were to be withdrawn from the study. Treatment of hyperplasia was dependent on the severity of their diagnosis and was based on the prudent medical judgment of the investigator. The protocol recommended that minimally , women with a diagnosis of simple hyperplasia without atypia or proliferative endometrium at the end of the study receive 10 mg/day of medoxyprogesterone acetate(MPA) for 14 days; whereas, women diagnosed with hyperplasia, other than simple without atypia, receive 40 mg/day of Megace (megestrol acetate) for three months.

If a biopsy was refused at study termination, and the TVS revealed an endometrial thickness < 5 mm, no treatment was required. If the TVS thickness was >5mm, but < 10 mm it was recommended that the patient receive 10 mg of MPA for 14 days with a follow-up sonogram in 3 months. If the TVS thickness was > 10mm, a 3 month course of Megace was recommended with a follow-up sonogram.

Comment: This type of treatment plan is consistent with present day(1998) medical treatment of hyperplasia. Additionally, with the lack of a biopsy and a TVS > 10 mm, treatment with Megace is optimal.

Safety

Safety parameters included: TVS, genital bleeding patterns, patch adhesivity, dermal patch tolerance, fractionated plasma lipid levels and a dietary recall questionnaire, incidence of AEs, clinical evaluations (including changes in vital sign measurements, weight, physical examination, mammography, and PAP smear results), and laboratory evaluations [including: hematology, serum chemistry, urinalysis, FHS level, sex hormone binding globulin (SHBG) levels, measurement of coagulation (anti-thrombin III, fibrinogen), and metabolic parameters (insulin and glucose)]

8.1.3.3

A sample size of 91 patients per treatment group assured 90% power to detect a difference between E_2/NETA patch treatment group and the E_2 only treatment group, assuming overall rates of hyperplasia of 12% for the E_2 only treatment group and a 1% rate for the E_2/NETA patch treatment group, and using a Bonferroni-adjustment on the p-value (i.e. testing at a 0.167 level, rather than the 0.05 level). This assumes a one-sided test, since(according to the sponsor) there has been ample literature to support the endometrial protective effect of progestins.

Comment: The sponsor was told in a pre-NDA meeting that pair-wise step-down two-sided test was preferred. One-sided test could be submitted since derived data was already being formulated. However, FDA statisticians perform 2-sided tests and this data would be evaluated as a 2-sided test.

As previously stated, 600 patients were planned to be enrolled in order to complete 400 (100 per treatment group) patients in anticipation of as many as 33% of enrolled patients being indeterminate for analysis.

A Fisher's Exact Test was used to analyze the incidence of endometrial hyperplasia between the estrogen-only group and the E_2 /NETA treatment groups. The Pair step-down Procedure was used to maintain a family-wise error(FWE) rate of 5%. With this procedure, each of three comparisons was done sequentially, using a 5% significance level.

All other comparative effects such as hot flushes, bone markers, demographic and baseline variables used two-way analysis of variance(ANOVA). For categorical the Cochran-Mantel-Haenszel test was used.

8.1.4 Results

Efficacy

There were 646 patients enrolled into this double-blind, controlled study at 33 centers in the U.S. The number of patents enrolled at any one center ranged from 6 to 36 patients , most sites (20 of 33) enrolled approximately 20 patients each. There were 163 patients enrolled in the E_2 50 group, 162 patients enrolled in the 50/140 group, 163 were enrolled in the 50/250 group and 158 were enrolled in the 50/400 group. Table 7(from the sponsor) shows the patient disposition in this study:

Table 7

Overall Study Completion and Summary of Reasons For Discontinuations From Study—ITT Population

Study 201

	E_2 50	E_2/NETA			Total
		50/140	50/250	50/400	
	N=163	N=162	N=163	N=158	N=646
	n(%)	n(%)	n(%)	n(%)	n(%)
Patients Randomized	163(100)	162(100)	163(100)	158(100)	646(100)
Patients Completing Study	102(63)	118(73)	112(69)	120(76)	452(70)
Total Patients Discontinued from Study	61(37)	44(27)	51(31)	38(24)	194(30)
PRIMARY REASON FOR DISCONTINUATION					
Lost to Follow-up	3(2)	5(3)	4(2)	5(3)	17(3)
Adverse Clinical Experience[1]	50(31)	19(12)	33(20)	23(15)	125(19)
Adverse Laboratory Experience	0(0)	0(0)	0(0)	0(0)	0(0)
Deviation form Protocol	2(1)	5(3)	3(2)	0(0)	10(2)
Consent Withdrawn	5(3)	12(7)	8(5)	7(4)	32(5)
Other	1(1)	3(2)	3(2)	3(2)	10(2)

[1]Includes discontinuations due to clinical adverse experiences or application site reactions

Note: as predicted, approximately 30% of patients discontinued from this study. The highest percent was in the placebo group and the lowest percent was the 50/400 group.

Baseline demographics showed the majority of the patients were Caucasian (approximately 90%) with approximately 4% Black, 2.6% Hispanic and 2.4% Oriental. Baseline characteristic showed the treatment groups were comparable with respect to race, age baseline hot flushes, BMI, tobacco use years since menopause, alcohol use, prior HRT use, height, weight and FSH levels. Patients mean age was 55.2 years, with a range of 39 to 69 years. The BMI values indicated an appropriate weight to height ratio. Forty-four to 49% of patients had prior use of HRT, and the mean or average number of years since menopause was approximately 7 years. FSH levels were all in excess of 100 mIU/mL for each treatment group. Seventeen to 23% of all patients used tobacco.

Screening endometrial biopsies were reviewed for study entry by Pathologist A who found no patients with endometrial hyperplasia. After enrollment, Pathologist B reviewed slides from all enrolled patients and determined that one patient in the 50/140 group) had complex hyperplasia without atypia. This patient was included in the study analysis because she received study drug. Pathologist C confirmed this patient had hyperplasia at screening.

At baseline, endometrial thickness averaged less than 4 mm for patients in all treatment groups. Additionally, 23% to 32% of patients in any group had an abnormal mammogram at baseline, but only one patient was considered to have a clinically significant abnormal mammogram. Although 6% to 8% of patients had PAP smear abnormalities, all patients were judged to be clinically acceptable for the study.

Compliance was defined as the patient wearing the patch for at least 21 of the 28 days per cycle. With this definition in mind, the number of compliant patients were comparable across all study groups, and ranged from 93% to 100% in each group for Cycles 1-13.

Results of the primary efficacy variable, reducing the incidence of estrogen induced hyperplasia are shown in Table 8 below:

Table 8
Study 201
Incidence of Endometrial Hyperplasia—ITT at One Year Population

HYPERPLASIA AT ONE YEAR	E_2 50	E_2/NETA		
		50/140	50/250	50/400
	N=163	N=162	N=163	N=158
N'	115	117	113	117
n(%)	23(20.00)	1(0.85)	1(0.88)	1(0.85)
p-value	NA	<0.001*	<0.001*	<0.001*

p-value from one-sided Fisher's exact test, using pair wise step-down procedure to adjust for multiple comparisons
N = Number of patients in the "ITT" population
N'= number of patients evaluated in the "ITT" at one year population"
n(%) = number (percentage) of patients with hyperplasia

- Post-Hoc evaluation using two-sided test with Bonferroni adjustment are identical to one year ITT population

At first glance, endometrial data appears to be quite favorable for patients who received NETA. However, this data is somewhat diminished by two tables presented by the sponsor which showed patients excluded from the ITT population. The sponsor presented table A1.4.1 and Table A2.3 (not reproduced) which showed the number of patients excluded from the ITT population. This number was substantial: 184 (28%) of patients. The primary reason reported for not being included in the ITT population was *no endpoint*

biopsy. The endpoint biopsy was defined as a biopsy obtained on or after cycle 12 or a biopsy which diagnosed hyperplasia before cycle 12. Forty-eight (27.78%) of patients were excluded from the E_2 group, and 45 (27.78%), 50(30.67%), and 41 (25.95%) were excluded from the 50/140, 50/250, and 50/400 groups, respectively. Of this 184 patients, 101 were excluded because they had only a baseline biopsy. Nineteen were in the E_2/50 group and 29, 30, and 23 were in the 50/140, 50/250, and 50/400 groups respectively. Of the 23 positive biopsies obtained from the $E_2$50 group, 10 were obtained before cycle 12 and 13 were obtained after cycle 12. Both positive biopsies obtained in the 50/140 group and the 50/400 group were obtained after cycle 12. Eighty biopsies were obtained prior to cycle 12, and 3 patients were not included because they did not have biopsy data. Of the remaining patients, eighty patients had a biopsy prior to cycle 12 and three treated patients were not in their appropriate biopsy group.

Comment: To have no biopsy data in the ITT population in 28% of patients is very disappointing and clearly shows the difficulty in requiring patients to remain in a yearly study and the difficulty in obtaining all biopsies prior to exit from the study.

As previously mentioned, two pathologists read all 462 slides. There was general agreement in greater than 96 percent of all slides between pathologist A and B. Pathologist C read 16 biopsies for which there was a disagreement between pathologist A and B. Pathologist C confirmed hyperplasia in 13/16 biopsies in which A and B disagreed. For four (25%) patients, pathologist C confirmed the diagnosis of pathologist A (1 hyperplasia, 3 no hyperplasia). For 12 (75%) patients, pathologist C confirmed the diagnosis of pathologist B (hyperplasia); pathologist A had previously determined there was no hyperplasia in these 12 patients.

Comment: This clearly shows the difficulty in reading endometrial slides and the differences in interpretation between three of the best gynecological pathologists in the country. This validates the reasoning for having three pathologists read the slides and a tie-breaker system to confirm a diagnosis.

Proliferative endometrium was the most common diagnosis made by both pathologist A and B(73.9% and 56.5%), respectively) in the E_2 group. For the E_2/NETA groups, pathologist A and B both diagnosed an increasing percentage of secretory endometrium and a decreasing percentage of proliferative with increasing NET dose. One patient in the E_2 50 group was noted to have simple hyperplasia with atypia by pathologist A who appeared to be least inclined of the three pathologist to diagnose hyperplasia. In addition, one patient in the 50/250 group was found to have hyperplasia in an endometrial polyp, as confirmed by 2/3 pathologist; this was not counted as a positive biopsy, however, since it did not occur in the endometrium.

The sponsor included secondary efficacy data in patients with hot flushes, intensity of hot flushes, intensity of sweating, and bone markers(both bone resorption and bone formation). This data will be briefly summarized:

A. The sponsor obtained hot flush data in the ITT population at cycles 3, 6, 9, and 12. The number of patients in each group ranged from 12 to 21. Patients on average had between 12-13 hot flushes per day at baseline. At cycles 3, 6, 9, and 12 hot flushes were decreased in all treatment groups by an average of -11.40 to -12.28 at cycle 3 to a -11.61 to -12.44 at cycle 12. Of interest, is the decrease to roughly 2 hot flushes per day compared to the four hot flushes per day in the placebo controlled studies. This could be interpreted as an effective of a comparative study, or the fact that patients were less symptomatic at entrance into this study.

B. The intensity of daily hot flushes was rated on a scale of 0 (none) to 3 (severe). For patients with at least 8 hot flushes per day at baseline and hot flushes at cycle 3, the intensity of hot flushes was mild to moderate (score1.44 to 1.78) at baseline and was reduced to none (score < 0.5) by cycle 3.This reduction in intensity was maintained from cycle 3 through cycle 12.

C. The intensity of sweating was recorded on a scale of 0 (none) to 3 (severe). For patients with at least eight hot flushes per day at baseline, and sweating present at cycle 3, the intensity of sweating was mild to moderate(score 1.33 to 1.69) at baseline and was reduced to none (0.33) by cycle 3 and was maintained through cycle 12.

D. The adjusted mean percent change in bone resorption markers(C-telopeptide and N-telopeptide to creatinine ratios) in the ITT population from baseline to Week 52 was reported in sponsor' table 13 (not reproduced). The number in each treatment group ranged from 100 to 111 patients. Adjusted mean changes range from -41.21% to -55.75% for C-telopeptide/creatinine ratio in the four treatment groups, with the largest change in the 50/400 group. For the N-telopeptide/creatinine ratio, the adjusted mean changes ranged from -30.65% to -44.26%, again with the largest change in the 50/400 group. The E_2 arm was noted to have the least effect on resorption markers, suggesting an additive effect of the progestin on bone resorption markers.

E. The adjusted mean percent change in bone formation markers (bone-specific alkaline phosphatase and osteocalcin) in the ITT population from baseline to Week 52 was reported in sponsor's table 14 (not reproduced). The number of patients in each group ranged from 105 to 116 patients. Adjusted mean changes ranged from -7.94 in the E_2 50 to -22.86 in the 50/400 group. Percent changes were statistically significant in the 50/140 and 50/400 group compared to the $E_2$50 group. The bone osteocalcin was also measured. The number of patients ranged from 103 to 117 per group. Adjusted percent change ranged from a -25.79% to a -30.44% per group. There were no statistically significant changes noted between groups.

F. Lipid parameters were reported from baseline to week 52. When compared to the E_2 50 patch, total cholesterol decreased 4% to 9% in the 50/140 and 50/250 groups $p<0.05$; triglycerides decreased 8.23% to 14.10% in the 50/140 and 50/250 group, respectively, $p<0.05$; LDL cholesterol decreased -1.16% in the 50/140 and -6.76% in the 50/250 groups, respectively, $p<0.013$; HDL cholesterol decreased -4.49% to -8.94% in the 50/140 group and the 50/250 groups, respectively, $p<0.001$. Although most of these values are statistically significant, the clinical significance in support of a labeling claim is doubtful, since some of the results (such as falls in cholesterol and LDL) are known to have a positive cardiovascular effect, while other results (such as fall in HDL) may have a negative effect. Thus, the actual significance of these changes is unclear.

Safety

All patients who were randomized and wore at least one patch (ITT population) were included in the safety analyses. In total, 646 patients (162 in the 50/140 group, 163 in the 50/250 group, 158 in the 50/400 group, and 163 in the $E_2$50 group) were evaluated for safety. Patients wore their patches between 284 to 296 days out of perfect 364 patch-wear days.

Adverse experiences were classified into a standardized terminology using the COSTART Coding Symbols for Thesaurus of Adverse Reactions. Each patient was counted only once in the incidence count for that preferred term.

Systemic adverse experiences were reported at least once in 154 (94%) of patients in the E_2 50 group, 152 (94%) of patients in the 50/140 group, 154 (94%) of patients in the 50/250 group, and 149 (94%) of patients in the 50/400 group. Overall, 94% of patients in the E_2 50 group reported AEs while 94% of patients in the E_2 NETA groups active reported AEs. The majority of these AEs were reported to be mild to moderate in severity.

In sponsor's table 26 (not reproduced) the incidence of systemic adverse reactions equal to or > 5% were reported. Symptoms related to the urogenital system were reported in 72% to 84% of the treatment groups. As in prior studies, breast pain, dysmenorrhea and menstrual disorders were reported in higher percentages in the E_2 NETA groups than the E_2 50 group. Headache was reported in 23% to 29% of all groups and rhinitis was reported in > 20% of all groups.

Under urogenital, breast pain was reported in 67 (41%) of the E_2 50 group and in 65 (40%), 77 (47%) and 90(57%) of patients in the 50/140, 50/250 and 50/400 groups respectively; dysmenorrhea was reported in 28(17%) of the E_2 50 group and in 58(36%), 64(39) and 68(43%) of the 50/140, 50/250, 50/400 groups respectively; menstrual disorder was reported in 25(15%) of patients in the E_2 50 group and in 39(24%), 38(23%) and 44(28%) of the E_2 NETA groups respectively; leukorrhea was reported in 7% to 14% of patients per group; vaginitis was reported in 10% to 17% of patients per group.

Under body as a whole, headache was reported in 38(23%) of patients in the E_2 50 group and in 40(25%), 29(18%), and 38(24%) of patients in the 50/140 group, 50/250 and 50/400 groups respectively; pain was reported in 23(14%) of patients in the E_2 50 group and in 31(19%), 28(17%) and 20(13%) of patients in the 50/140, 50/250 and 50/400 groups respectively; back pain was reported in 25 (15%) of patients in the E_2 50 group and in 26(16%), 22(13%) and 36(23%) of patients in the 50/140, 50/250, and 50/400 groups respectively; asthenia was reported in 13(8%) of E_2 50 patients and in 18(11%), 23(14%), and 24(15%) of the E_2 /NETA groups respectively; under Nervous system, depression was reported between 8% to 9% of all treatment groups; insomnia was reported between 6% and 10% of all treatment groups; under Respiratory system, rhinitis was reported between 20% and 25% of all treatment groups; sinusitis was reported in 10% to 15% of all treatment groups; under Skin and Appendages, application site reaction were reported between 13% and 18% of all treatment groups; AEs related to the cardiovascular, endocrine, hemic and lymphatic system, and special senses occurred in less than 5% of patients in any group.

In assessing AEs pertinent to a combination patch, or any HRT therapy, the incidence of endometrial hyperplasia, bleeding/spotting patterns, the incidence of amenorrhea, whether the estrogen/progestin is give sequentially or continuously, patch adhesivity and patch site reactions are most important. Average endometrial thickness generally increased in all treatment groups over the 13 study cycles. At baseline average endometrial thickness was approximately 4 mm for each group. In sponsor's table A11.2 endometrial thickness was reported for each treatment group. Thirty-seven (5.72%) biopsies were missing out of the 646 evaluable patients. A low of seven (4.2%) were missing in t he E_2 group compared to 11 (6.79%) in the 50/140 group. Increasing endometrial thickness of > 5-8 mm was reported in 34 (20.86%) of the E_2 group and in 26 (16.05%), 39 (23.93%) and 45(28.48%) of the 50/140, 50/250 and 50/400 groups respectively. Endometrial thickness of > 8 mm was reported in 476 (28.83%) of the E_2 group and 18(11.11%), 24 (14.72) and 21(13.29%) of the 50/140, 50/250 and 50/400 groups respectively. There were two biopsies $\leq$ 5 mm that were positive for endometrial hyperplasia, one in the E_2 only group, and one in the 50/140 group; there were also three positive biopsies from the > 5-8mm group, three in the E_2 group and one in the 50/400 group. Importantly, this shows that TVS of $\leq$5 mm can be positive for endometrial hyperplasia in a range of 1.5% to 3.2% in the E_2 group and 50/140 group respectively, and that biopsies in the 5 to 8 mm range were positive in 3.3% in the 50/400 group and 12% in the E_2 group.

Comment: This data suggests that patients with a TVS endometrial thickness < 8mm, even with the use of a progestin such as NETA, are at approximately a 1-3% risk of developing hyperplasia(sequential method).

The incidence of bleeding/spotting was recorded for Cycles 2, 5, 8, and 11. The incidence of withdrawal bleeding/spotting was similar across the three E_2NETA active group and across cycles. Withdrawal bleeding occurred in about two-third of the E_2 NETA patients at each cycle in each group. The majority of patients 59% to 76% in each E_2NETA group experienced withdrawal bleeding or spotting in Cycles 10, 11, or 12. The percentage of women who had irregular bleeding/spotting in any cycle 1 to 12 ranged from 18%-24% in the 50/140 group, from 23%-35% in the 50/250 group, from 19%-31% in the 50/400 group, and from 11% to 44% in the E_2 50 group.

The incidence of amenorrhea decreased in all group over Cycles 1 to 12, but was higher in the E_2 group (range 56%-89%) than for any E_2 NETA group(range 2% to 21%) at any of these cycles. Within the E_2 NETA groups, the 50/140 group had a higher incidence of amenorrhea and generally a slightly lower incidence of irregular bleeding/spotting than either of the 50/250 or 50/400groups. When the duration of menopause was greater than 3 years, in the 50/140 group, a higher incidence of amenorrhea was noted and lower incidence of irregular bleeding/spotting than in women who were within 3 years of menopause.

Patterns of bleeding/spotting were similar from cycle to cycle for each E_2 NETA group and were consistent with a withdrawal bleeding pattern. The peak percentage of patients with bleeding/spotting on a given day occurred earlier in the 50/140 group (days 25-26) than in the 50/400 group (days 4-5 of the next cycle). In the E_2 group, as expected, there was no cyclic bleeding pattern noted. At cycle 12, the mean number of day bleeding/spotting ranged from 5.8 to 7.1 days/cycle in the E_2 NETA groups compared to 12.0 days/cycle in the E_2 50 group.

Patch adhesivity was evaluated by the reviewing investigator who assessed adherence and examined patient diary data. In this sequential wear study, the E_2 50 patch was adhered >90% of the time in 94% of patients, and between 89% to 92% of the E_2 NETA groups. There was incomplete adherence (75% to 90%) in 3% of the E_2 50 group and 5% to 7% of the 50/140 to 50/400 groups. The E_2NETA active patches "fell off" on average less than 1% of the days worn compared to the E_2 50 patch which "fell-off" 3% of the days worn. Of the active groups, 25% of the E_2 50 group and 26% of the E_2 400 group had an unscheduled patch removal, while the 50/140 and 40/250 had unscheduled removal rates of 15% to 16%.

The incidence of application site reaction AEs as assessed by the investigator ranged from 12% in the E_2 50 group to 11 to 14% for the E_2 NETA patches. Application site reaction was slightly lower for both E_2 NETA placebo patches than the E_2 50 patches.

Erythema was the most common reported component of an application site reaction. Eight percent of the E_2 NETA groups reported erythema and 10% of the E_2 50 group. Severe application site reactions (fissuring and or scaling/glazing) were reported for one (1%) patient in both the 50/400 and E_2 50 treatment groups. Overall, , 8(2%) of the patients in the E_2 NETA groups combined compared to 3(2%) in the E2 50 group discontinued due to an application site reactions.

8.1.5 Reviewer's comments/conclusion of study results

In this randomized, double-blind, estrogen-only arm controlled study, three doses of E_2 NETA were compared to an estrogen-only arm. The primary efficacy parameter was the incidence of endometrial hyperplasia produced in the ITT population at the end of 13- 28 day treatment cycles. The estradiol-only group had a 20% incidence of endometrial hyperplasia after one year and the three estrogen/progestin groups had 1% or less endometrial hyperplasia ($p<0.001$). One must consider these results in light of the fact that 184(28%) of patients could not be included in the ITT population at one year, primarily because of no baseline biopsy(N=101) and biopsies which were obtained prior to cycle 12(n=80). Breast pain, pain, dysmenorrhea, menstrual disorder(specifically significant bleeding/spotting), back pain, headache and application site reactions are seen in significant numbers, as was seen in the VMS studies. Bleeding disorders appear to be greater with increasing NETA doses. Application site reactions, such as skin irritation were noted in 11% to 14% of patients. Approximately, 2% of patients discontinued use of their patches because of an application site reaction. Lipid parameters were generally lower, however, this also included lower HDL values, which may counteract some of the potential cardiovascular benefits that might otherwise have been anticipated. Bone marker changes are not suggestive of any significant deleterious effect when compared to estrogen alone, and in fact, may suggest an enhanced effect. Overall, endometrial hyperplasia is significantly reduced when compared to an estrogen-only treatment arm.. Bleeding and application site reactions may be a compliance concern with the use of these patches, more than other patches.

Study 202 (Endometrial Protection)

8.1.1 Objective/rationale

The primary objective of this study was to evaluate the efficacy and safety of three doses of norethisterone (NETA) when administered continuously with estradiol compared to estradiol alone, on the incidence of estrogen-induced endometrial hyperplasia. Secondary objectives of this study include evaluation of the effect of three doses of NETA when administered continuous E_2, compared to E_2 alone, on the following parameters: genital bleeding, vasomotor symptoms, lipid profiles, selected parameters of metabolism and coagulation, bone biochemical markers, dermal patch tolerance, patch adherence, laboratory and clinical safety parameters, selected QOL indices, and serum concentrations of E_1, E_2, and NET.

8.1.2

Design

This was a multicenter, randomized, double-blind, estrogen-only arm controlled study designed to evaluate the safety and endometrial protection of three doses of E_2 NETA patches (50 mcg E_2 in combination with either 140, 250 or 400 mcg/day NETA) when given in a continuous wear regimen.

Inclusion Criteria:

Are identical to study 201

Exclusion Criteria:

Are identical to study 201

Patients were withdrawn from the study if:

See Studies 303 and 304. In addition, patients could also be withdrawn for the following:

- on study development of biopsy-proven endometrial hyperplasia occurred;
- they received concurrent chronic (longer than 10-day duration over the entire study period) system glucocorticoid therapy.

Study Procedures:

Are identical to study 201 with the exception that patches were changes every 3.5 days and were worn continuously. In the event that a patch "fell off" at an unscheduled patch wear time, the same kin of patch was applied from the appropriate replacement "spare" patch supply. After replacement, the patch changed according to the original schedule.

8.1.3.2

Efficacy

Is essentially the same as outlined in study 201

Safety

Is essentially the same as outlined in study 201

8.1.3.3

Sample size and statistical methods are identical to study 201

Results:

Efficacy

There were 625 patients enrolled into this double-blind, controlled study at 37 centers in the US. The number of patients enrolled at any one center ranged from 7 to 33; most sites (23 of 37) enrolled approximately 20 ($\pm$ 4) patients each. There were 155 patients enrolled in the E_2 50 group, 163 enrolled in the 50/140 group, 149 enrolled in the 50/250 group, and 158 enrolled in the 50/400 group. Table 9(from the sponsor) shows discontinuation from the study and the ITT population:

Table 9

Overall Study Completion and Summary of Reasons For Discontinuations From Study---ITT Population

Table	E_2 50	E_2/NETA			Total
		50/140	50/250	50/400	
	N=155	N=163	N=149	N=158	N=625
	n(%)	n(%)	n(%)	n(%)	n(%)
Patients Randomized	155(100)	163(100)	149(100)	158(100)	625(100)
Patients Completing Study	76(49)	123(75)	99(66)	93(59)	391(63)
Total Patients Discontinued from Study	79(51)	40(25)	50(34)	65(41)	234(37)
PRIMARY REASON FOR DISCONTINUATION					
Lost to Follow-up	2(1)	1(1)	4(3)	4(3)	11(2)
Adverse Clinical Experience[1]	59(38)	24(15)	42(28)	46(29)	171(27)
Adverse Laboratory Experience	0(0)	0(0)	0(0)	0(0)	0(0)
Deviation from Protocol	5(3)	4(2)	2(1)	4(3)	15(2)
Consent Withdrawn	6(4)	7(4)	1(1)	7(4)	21(3)
Other	7(5)	4(2)	1(1)	4(3)	16(3)

[1] Includes discontinuation due to clinical adverse experiences or application site reactions

Note: Approximately 37% of patients discontinued from this study. The highest percent was in the E_2 50 group and the lowest percentage was in the 50/140 group. AEs and discontinuation rates are higher than those seen in the sequential study (201). This is somewhat surprising, since the sequential regimen should produce more predictable bleeding, while the continuous method produces less bleeding over time and is more tolerable and desirable to the postmenopausal women.

Baseline demographics showed the majority of patients were Caucasian (approximately 84%), 5% were Black, 3% were Oriental and 8% were Hispanic. Patients were on average, 54 to 55 years of age, although ages ranges from 39 to 70 years. The BMI indicated an appropriate weight to height ratio. Twelve percent to 18% of all patients used tabacco. Between 28% and 42% of patients had used prior HRT, with the highest percentage 42% in the E_2 50 group. The previous duration of prior use ranged from 42 months to 64 months in the E_2 50 group. FSH levels were in the 100 to 109 mIU/mL range, validating the postmenopausal status of the patients.

Screening endometrial biopsies were reviewed for study entry by pathologist A who found no patients with endometrial hyperplasia. After enrollment, pathologist B reviewed slides from all enrolled patients and determined that one patient in the 50/250 group) had hyperplasia in an endometrial polyp at screening. Pathologist C confirmed the presence of hyperplasia at screening; however, the hyperplasia was diagnosed within the endometrium instead of within an endometrial polyp. There were no other cases of hyperplasia diagnosed at screening.

At baseline, endometrial thickness averaged slightly more than 4 mm for patients in all treatment group (ITT population). Most patients in all treatments groups have normal mammograms and PAP smears. However, baseline abnormalities were noted for 20% to 31% of patients in any group; no abnormalities were considered clinically significant by the investigators. One patient was noted to have microcalcifications at screening mammogram and entered the study, further examination revealed lobular carcinoma-in-situ and this patient was discontinued from the study. Pap smear abnormalities were noted in 3% to 5% of patients in any group at baseline. All patients had PAP smear findings judged to be clinically acceptable by the investigator for study entry.

Compliance was defined as the patient wearing the patch for at least 21 of the 28 days per cycle. With this definition in mind, the number of compliant patients were comparable across all study groups, and ranged from 92% to 100 percent from cycle 1 through cycle 14. There was one patient in cycle 15 in the 50/140 group.

Results for the primary efficacy variable, the incidence of estrogen-induced hyperplasia, are shown in table 10 below:

Table 10
Study 202

Incidence of Endometrial Hyperplasia—ITT at One Year Population

HYPERPLASIA AT ONE YEAR	E_2 50	E_2/NETA		
		50/140	50/250	50/400
	N=155	N=163	N=149	N=158
N[1]	102	123	97	89
n(%)	39(38.00)	1(0.81)	1(1.03)	1(1.12)
p-value	NA	<0.001*	<0.001*	<0.001*

p-value from one-sided Fisher's exact test, using pair wise step-down procedure to adjust for multiple comparisons
N = Number of patients in the "ITT" population
N[1]= number of patients evaluated in the "ITT" at one year population"
n(%) = number (percentage) of patients with hyperplasia

- Post-Hoc evaluation used two-sided test with Bonferroni adjustment are identical to one year ITT population

Note: The patient with the disputed baseline biopsy was confirmed as having endometrial hyperplasia. This patient has been included into Table 10 because the patient received drug (single case noted in the 50/250 arm). In the evaluable population, this patient can be excluded and the p-value remains <0.001.

Endometrial data appears to be quite favorable for patients who received NETA. However, this data needs to be considered in light of two tables presented by the sponsor which showed patients excluded from the ITT population. The sponsor presented table A1.4.1 and table A2.3(not reproduced) which showed the number of patients excluded from the ITT population. This number is substantial: 214(34%). The primary reason reported for not being included in the ITT population is *no endpoint biopsy. The endpoint biopsy*

was defined as a biopsy obtained on or after cycle 12 or a biopsy which diagnosed hyperplasia before cycle 12. Fifty-three (34.10%) were excluded from the E_2 50 group, and 40 (24.54%), 52(34.90%), and 69(43.67%) were excluded from the 50/140, 50/250 an 50/400 groups, respectively. Of this total, 99 had only a baseline endometrial biopsy and 105 were not included because they had a biopsy before cycle 12 that did not show hyperplasia and no biopsy during cycles 12 through 14. Nine additional patients had no biopsy data in their treatment group and one patient was missing baseline data.

Comment: Having insufficient biopsy data in 34% of patients is very disappointing, but shows the difficulty in requiring patients to remain in a yearly study and the amount of diligence that is needed to obtain all biopsies prior to exit from the study.

Two pathologists reviewed all 411 available endometrial biopsies. There was general agreement between pathologist A and pathologist B on 94% of all biopsies read. The third pathologist read 23 biopsies for which there was a disagreement between pathologist A and pathologist B. Pathologist C confirmed hyperplasia in 22 of the 23 biopsies in which pathologist A and B had disagreed.

Proliferative endometrium was the most common diagnosis made by both pathologist A and pathologist B (65.7% and 43.1%, respectively) for the E_2 50 group. For the E_2NETA groups, pathologist A diagnosed an increasing percentage of atrophic endometrium and a decreasing percentage of proliferative endometrium with increasing NETA dose. Pathologist B diagnosis of "atrophic endometrium" decreased with increasing NETA dose in the majority (more than 60%) of women in each E_2NETA group.

The sponsor included secondary efficacy data in patients with hot flushes, intensity of hot flushes, intensity of sweating, and bone markers (both bone resorption and bone formation). These data will be briefly summarized:

A. The sponsor obtained hot flush data in the ITT population at cycles 3, 6, 9, and 12. The number of patients in this small subset ranged from 8 to 18. Patients averaged between 11 and 12 hot flushes per day at baseline. At cycles 3, 6, 9, and 12 hot flushes decreased in all treatment group by an average of -9.60 to -12.11 at cycle 3 to a -8.97 to -12.04 hot flushes per day at cycle 12 from baseline. The lowest reduction were noted in the 50/140 group and the highest reduction was noted in the 50/400 group.

B. The intensity of daily hot flushes was rated on a scale of 0 (none) to 3 (severe). For patients with at least 8 hot flushes per day at baseline and hot flushes at cycle 3, the intensity of hot flushes were mild to moderate (score1.1 to 1.8) at baseline was reduced to none(score <0.4) by cycle 3. The reductions in intensity were maintained from cycle 3 through cycle 12.

C. The intensity of sweating was recorded on a scale of 0 (none) to 3 (severe). For patients with at least eight hot flushes per day at baseline, and sweating at cycle 3, the intensity of sweating was mild to moderate (score 1.2 to 2) at baseline and was reduced to none (score < 0.4) by cycle 3. The reductions were maintained from cycle 3 through cycle 12.

D. The adjusted mean percent change in bone resorption markers (C-telopeptide and N telopeptide to creatinine ratios) in the ITT population from baseline to week 52 were reported in sponsor's table13(not reproduced). The number in each group ranged from 75 to 120 patients. Adjusted mean changes ranged from -16.87 to -44.16 for C-telopeptide/creatinine ratio in the four treatment groups with the largest change in the 50/400 group. The smallest change was in the 50/140group and this was statistically significant from the $E_2$50 group. For the N-telopeptide/creatinine ratio, the adjusted mean changes ranged from -15.51 to a -38.05. The smallest percent change was noted in the 50/140 group and the largest change was in the E_2 50 group.

E. The adjusted mean percent change in bone formation markers (bone-specific alkaline phosphatase and osteocalcin) in the ITT population from baseline to week 52 was reported in sponsor's table 14 (not reproduced). The number of patients in each group ranged from Adjusted mean percent changes ranged from -16.19 to -25.80, with the largest smallest decrease in the50/140 group and the largest in the 50/400 group. Bone osteocalcin was measured. The number of patients ranged from per group. Adjusted percent change ranged from a · The decrease in osteocalcin recorded for the 50/140 group was statistically significant less than the decrease noted for the E_2 50 group at week 52.

Safety

All patients who were randomized and wore at least one patch (ITT population) were included in the safety analyses. In total, 625 (163 in the 50/140 group, 149 in the 50/250 group, 158 in the 50/400 group, and 155 in the E_2 50 group) were evaluated for safety.

Adverse experiences were classified into a standardized terminology using the COSTART Coding Symbols for Thesaurus of Adverse Reactions. Each patient was counted only once in the incidence count for that preferred term.

Systemic adverse experiences were reported at least once in 146 (94%) of patients in the E_2 50 group, 152(93%) of patients in the 50/140 group, 142(95%) of patients in the 50/250 group, and 150(95%) of patients in the 50/400 group. Overall, 94% of patients in the $E_2$50 group and 94% of patients in the E_2NETA group reported AEs. The majority of these AEs were noted to be mild to moderate in severity.

Sponsor's table 27 (not reproduced) reported the incidence of systemic adverse reactions equal to or > 5%. Symptoms related to the urogenital system were reported in 64% to 79% of the treatment groups, followed by body as a whole were 55% to 59% of patients in all treatments groups reported an AE. The most common AEs observed were breast pain, application site reaction, headache, and dysmenorrhea which were reported by 20% or more of the patients in any treatment group. Application site reactions occurred more often in each E_2NETA group (23% to 26%) compared to the $E_2$50 group(18%).

Under urogenital, breast pain was reported in 60(39%) of patients in the $E_2$50 group and in 45(28%), 72(48%) and 84(53%) of patients in the 50/140, 50/250, and 50/400 groups respectively; dysmenorrhea was reported in 31(20%) of patients in the $E_2$50 group and in 40(25%) 34(23%) and 43(27%) of the 50/140, 50/250, and 50/400 groups respectively; menstrual disorder was reported in 19(12%) of patients in the $E_2$50 group and in 15(9%), 21(14%) and 19(12%) of patients in the 50/140, 50/250, and 50/400 groups respectively; menorrhagia was reported in 13(8%) of patients in the $E_2$50 group and 1`% to 3% of the E_2NETA groups; endometrial hyperplasia was reported in 31(20%) of patients in the $E_2$50 group and in 1% or < of the E_2NETA groups;

Under body as a whole, headache was reported in 30(19%) of patients in the $E_2$50 group and in 40(25%), 25(17%), and 28(18%) of patients in the 50/140, 50/250, and 50/400 groups respectively; pain was reported in 17(11%) of patients in the $E_2$50 group and in 30(18%), 18(12%), and 23(155) of patients in the 50/140, 50/250, and 50/400 group respectively; back pain was reported in 17(11%) of patients in the $E_2$50 group and in 22(13%), 23(15%), and 28(18%) groups respectively; asthenia was reported in 23(15%) of patients in the $E_2$50 group and in 13(8%),17(11%), and 10(6%) of patients in the 50/140, 50/250, and 50/400 groups respectively; under nervous system, depression was reported in 11(7%) of patients in the $E_2$50 group and in 14(9%) of patients in all three E_2NETA groups; under respiratory system, rhinitis was reported in 22(14%) of patients in $E_2$50 group and in 30(18%), 28(19%), and 24(15%) of patients in the 50/140, 50/250 and 50/400 groups respectively; sinusitis was reported in 18(12%) of patients in the $E_2$50 group and in 18(11%), 16(11%) and 10(6%) of patients in the 50/140, 50/250, and 50/400 groups respectively; under skin and appendages, application site reactions were reported in 27(17%) of patients in the $E_2$50 group and in 44(27%), 41(28%) and 68(43%) of patients in the 50/140, 50/250, and 50/400

groups respectively; AEs related to the cardiovascular, endocrine, hemic and lymphatic system, and special body senses occurred in less than 5% of patients in any group. Clearly, these AEs are similar whether the patients was in the estrogen-only arm or in one of the E_2/NETA groups.

In assessing AEs pertinent to a combination patch, or any HRT therapy, the incidence of endometrial hyperplasia, bleeding/spotting patterns, the incidence of amenorrhea, whether the estrogen/progestin is given sequentially or continuously, patch adhesivity and patch site reactions are most important. Average endometrial thickness as measured by TVS was slightly greater than 4 mm at baseline. At endpoint(table A11.1), endometrial thickness has increased from 4.10 to 4.63 in the 50/140 group, from in the 50/250 group, from in the 50/400 group, and from in the $E_2$50 group. Forty- four of 625 biopsies were missing. Biopsies were reported to be > 5 mm in 21.47% of patients in the50/140 group, 24.83% in the 50/250 group, 17.72 in the 50/400 group, and 17.72% in the $E_2$50 group. Importantly, one biopsy in the 50/400 group was positive for hyperplasia at < 5mm and one biopsy in the 50/140 group was positive for hyperplasia in the >5-8 mm group. One entrance biopsy was positive for hyperplasia in the 50/250 group. This patient should not have been entered into this study, but is included in the ITT analysis since she received study drug. Overall, with continuous E_2NETA the incidence of endometrial hyperplasia is approximately 1% for all treatment groups compared to 38% in the $E_2$50 group.

The incidence of bleeding/spotting was reported at least once during the study by 68% of patients in the 50/140 group, 90%in the 50/250 group, 93% in the 50/400 group and 79% in the $E_2$50 group. The mean number of days of irregular bleeding/spotting ranged from 10.6 episodes in the 50/250 group to 7.4 episodes in the $E_2$50 group. The mean number of days of irregular bleeding and/or spotting per episode was 4.4 days in the 50/140 group and highest at 6.8 days in the $E_2$50 group. Mean intensity of bleeding was moderate for all groups.

Amenorrhea has be shown to occur with long term administration of a continuous-combined oral estrogen and progestin regimen. The sponsor presented data(Table 17) on the first three cycles of treatment and the last three cycles. During cycles 1, 2, and 3, approximately half of the women were amenorrheic in both the $E_2$50 and the 50/140 group. During cycles 10, 11, and 12, the percentage of women who were amenorrheic had decreased to 35% in the $E_2$50 group, slightly increased from 48% to 53% in the 50/140 group, and increased from 15% to 39 % in the 50/250 group.

Comment: There is a substantial amount of patients still bleeding at one year. Roughly one-half of all patients will not achieve the amenorrheic state and were still bleeding/spotting after receiving treatment for one year. This is clearly more bleeding/spotting than the sponsor would have anticipated and would appear to be a potential compliance problem, since most women are desirous of amenorrhea at a higher rate than 45% to 60%.

Patch adhesivity was evaluated by the reviewing investigator who assessed adherence and examined patient diary data. In this continuous wear study, investigator's assessments showed patch adherence to be "complete" (defined as patch adhered >90%) for 83% to 90% of women. Placebo patches adhered in the 83% to 90% range. There was incomplete adherence(75% to 90%) in 5% to 7% of patches. Each of the active E_2NETA patches "fell off" less than 1% of the total days worn in this study. However, in sponsor's table 21(not reproduced) only 37(24%) of the E_2 50 patches never "fell off" and the E_2NETA patches "fell off" between 47% and 51% of the time. In addition, between 25% and 32% of all treatment groups("fell off" for 1 to 2 days of the treatment cycles. Unscheduled patch removal ranged from cycle days for the E_2NETA patches compared to 1.66 days for the $E_2$50 patch.

The incidence of application site reaction AEs assessed by the investigator ranged from 18(12%) in the $E_2$50 group to 41(26%) in the 50/400 group. Erythema was reported in 16(10%) of patients and in 27(17%) to 36(23%) of the E_2NETA groups. It appears that there are more incidences of skin reactions such as scaling/glazing, papules/vesicles, fissuring, and exudate/crusting than had been reported in the sequential method. Scaling/glazing was reported in 6% to 15% of patients. This was not seen with the E_2 50 patch.

Overall, 39(8%) of women in the E_2NETA groups combined compared to 5(3%) in the $E_2$50 group discontinued due to an application site reaction.

Lipoprotein data was included in the sponsor's safety analyses since with the use of oral contraceptives, long-term use of norethindrone and norethindrone acetate had been shown to decrease certain lipoproteins. The sponsor obtained baseline plasma lipid parameters and followed patient to week 52. Data shows total cholesterol decreased from a -2.02% in the $E_2$50 group and 5.43%, -8.53%, -14.02% in the 50/140, 50/250, and 50/400 groups respectively; triglycerides decreased a -6.66% in the $E_2$50 group and -4.62, -9.47 , and -19.03 in the 50/140, 50/250, and 50/400 groups respectively; LDL cholesterol decreased a -3.44% in the $E_2$50 group and a -4.62%, -7.64%, -11.22% in the 50/140, 50/250, and 50/400 groups respectively; HDL-cholesterol increased 7.30% in the $E_2$50 group and decreased -3.11%, -9.14%, and -14.80% in the 50/140, 50/250 and 50/400 groups respectively. Ratios of both TC/HDL-C and LDL-HDL-C decreased slightly for the $E_2$50 group and was unchanged in the 50/140 group. In the 50/250 group these ratios were unchanged and in the 50/400 group slightly increased.

Comment: There is clearly a negative trend for LDL and HDL cholesterol with an increasing dose of NETA. The sponsor will not market the 50/400 dose which appears to have the most negative effect upon lipoproteins. Although, total cholesterol was decreased to a statistically significant level in the 50/140 and 50/250 groups, this is not clinically significant in view of the negative effect upon HDL cholesterol of approximately 10%. This lack of an overall clinically significant effect on lipoproteins is seen in the TC/HDL-C and LDL-C/HDL-C ratios which either decreased slightly or remained unchanged.

8.1.5 Reviewer's comments/conclusion of study results

In this randomized, double-blind, estrogen-only controlled study, three doses of E_2/NETA were compared to an estrogen-only arm in a continuous wear regimen. The primary efficacy parameter was the incidence of endometrial hyperplasia produced in the ITT population at the end of 13-28 day treatment cycles. The estradiol-only group had a 38% incidence of endometrial hyperplasia after one year and the three estrogen/progestin groups had approximately 1% endometrial hyperplasia($p < 0.001$). While highly significant, it must also be noted that 214(34%) of patients could not be included in the ITT population at one year. Breast pain, dysmenorrhea, menstrual disorder (bleeding), back pain, headache, and application site reactions are seen in increasing numbers when compared to the sequential method. The incidence of amenorrhea had increased from 48% to 53% in the 50/140 group and from 15% to 39% in the 50/250 group when cycles 1, 2, and 3 are compared to cycles 10, 11, and 12. The incidence of endometrial hyperplasia is increased from 20% in the sequential-wear regimen. Application site reactions, such as skin irritation were noted in 12% to 26% of users. More severe skin reactions, including fissuring, scaling/glazing, and exudate/crusting were reported with the continuous wear method than the sequential method. Eight per cent of the E_2NETA groups discontinued due to an application site reaction compared to 2% in the estrogen-only group. Lipid parameters again show a beneficial decrease in LDL, but also a decrease in HDL, which is a concern. Overall, endometrial hyperplasia increased in the estrogen-only arm from 20% in the sequential study to 38% in the continuous study, however, the incidence of hyperplasia with CombiPatch remained at approximately 1% in both studies. Bleeding and application site reactions may be a compliance concern with the use of these patches.

9. Overview of Efficacy—Comparative results between studies

The sponsor conducted two randomized, double-blind, placebo-controlled studies (303-304) comparing the efficacy of three doses of an E_2NETA patch (140, 250, or 400 mcg/day) to placebo in two 12-week studies. Starting in the third treatment week and continuing through 12 weeks of treatment, both the frequency and severity of moderate to severe VMS symptoms were statistically significant improved compared to placebo. On average in the 303(sequential study) VMS were decreased by 4 per day compared to placebo and by 3 per day compared to placebo(continuous regimen). This compares favorably to other estrogen-only patches. Secondary efficacy parameters relating to a health-related QOL questionnaire showed variant

degrees of improved QOL in different treatment groups. This is consistent with other estrogen products, either oral or transdermal, which usually show variant degrees of improved QOL with estrogen replacement therapy. The sponsor elected not to pursue approval of the 400 mcg/day dose since there is no clinical difference in efficacy between doses.

The sponsor conducted two randomized, double-blind, estrogen-only arm controlled, 13-cycle (52 week) studies in four parallel treatment groups. Overall 1,271 women were entered into the ITT population. Of this total, 31.3% of patients were not included into the final ITT population because they had only a baseline endometrial biopsy, or had a biopsy prior to cycle 12 that did not show hyperplasia and no biopsy during cycles 12 thorough 14. In study 201, there were 23 (20%) patients in the estrogen-only arm who developed endometrial hyperplasia compared to one each in the 50/140 group, the 50/250 group and the 50/400 group. The E_2/NETA comparisons were all < 1% and significant at the $p<0.001$ level using a two-sided step-down multiple comparison procedure. When all three E_2/NETA groups are combined, the 95% confidence interval of the percentage of patients having endometrial hyperplasia at one year is (0.07, 2.07). In the 202 study, there were 39 (38%) of patients who developed endometrial hyperplasia in the estrogen-only arm and 1 in the 50/140 group, 1 in the 50/250 group and 1 in the 50/400 group. The E_2/NETA comparisons were 1/123 (0.81%) in the 50/140 group, 1/97(1.03%), and 1/89 (1.12%) in the 50/400 group, $p<0.001$ using a two-sided step-down multiple comparison procedure. If all three E_2/NETA groups are combined, the 95% confidence interval of patients having endometrial hyperplasia at one year is (0.2, 2.81%).

10 Overview of Safety

A total of 446 patients were randomized in the ITT population in studies 303 and 304. Both studies used the COSTART Coding Symbols for Thesaurus of Adverse Reactions Term, Third Edition. In study 303, 99 (93%) of placebo patients completed the study compared to 98(87%), 107(96%), and 107(94%) in the 50/140, 50/250, and 50/400 group, respectively. In study 304, 47(87%) placebo patients completed this study compared to 52(90%), 49(92%), and 55(90%) in the 50/140, 50/250, and 50/400 groups, respectively.

Deaths

No deaths were reported during this clinical program.

Significant/Potential Significant Events

In study 303, six patients discontinued due to an AE. Five of 6 patients were in the 50/140 group. Two of 5 patients in the 50/140 group were reported to have either endometrial hyperplasia or disordered proliferative endometrium, the other three patients had combinations of breast pain, dysmenorrhea or severe headaches. One patient in the 50/250 group discontinued due to severe dysmenorrhea and severe vaginal bleeding. In study 304, eight patients discontinued due to severe AEs. Two patients were in the placebo group, three patients were in the 50/140 group (one patient had dysmenorrhea, headache, and bloating, one patient had severe breast pain, and one patient had severe mood swings), one patient discontinued in the 20/250 group due to dysmenorrhea, and two patients discontinued in the 50/400 group due to depression, acne, and insomnia.

Systemic adverse experiences occurred in 78/107 (73%) of patients in the placebo group, 91/113(81%) of patients in the 50/140 group, 96/112(86%) of patients in the 50/250 group, and 96/114(84%) of patients in the 50/400 group. Headache, breast pain, and dysmenorrhea were reported in >20% or more of patients in any group. Menstrual disorder(variant types of menstrual bleeding) occurred in increasing percentages of patients with 16(14%) occurring in the 50/400 group compared to 2(2%) in the placebo group. Other conditions such as rhinitis, sinusitis, nausea, back pain, and asthenia occurred in >5% of patients, but this was not significantly greater than the placebo group. Depression occurred in a lesser number of patients in

the treated group than in the placebo group. The incidence of patch-site reactions AEs occurred in < 10% of all patients. Patch adherence(>90%) was reported in >90% of all patients. However, in study 301, 10% to 15% of patches "fell off" and in study 302, 13% to 29% of patches "fell off" during 1-3 days of the wear cycle. Overall, the incidence of systemic adverse experiences are similar to those reported with other estrogen-only products, and adverse experiences usually attributed to the progestin component in oral contraceptives were not well characterized in these studies.

A total of 1,271 patients were randomized to treatment groups in studies 201 and 202. Three-hundred-eighteen patients were enrolled in the estrogen-only arm, 325 were enrolled in the 50/140 group, 312 were enrolled in the 50/250 group, and 316 were enrolled in the 50/400 group. Adverse events were standardized using the COSTART system.

Deaths

No deaths were reported during this clinical program.

Significant/Potential Significant Events

In studies 201 and 202, a total of 296 patients(23.3%) were discontinued from these studies due to an AE. Of this total, 109(34%) were in the E_2 50 group, 43(13%) were in the 50/140 group, 75 (24%) were in the 50/250 group and 69(22%) were in the 50/400 group. The most frequent AEs leading to study discontinuation were vaginal hemorrhage (4%), application site reaction (4%), menorrhagia(3%) , and breast pain (2%). Most of these AEs were felt by the investigators as probably or possibly being related to study drug.

Systemic adverse experiences occurred in 300(94%) of patients in the $E_2$50 group, in 304(945) of patients in the 50/140 group, in 296(95%) of patients in the 50/250 group, and 299(95%) of patients in the 50/400 group. The urogenital system and the Body as a Whole had the highest percentages of patients with AEs. Within the urogential system, breast pain ranged from 34% in the 50/140 group to 55% in the 50/400 group, dysmenorrhea ranged from 19% in the $E_2$50 group to 35% in the 50/400 group, endometrial hyperplasia ranged from 12% in the $E_2$50 group to <1% in each treatment group, menstrual disorder(bleeding) ranged from 14% in the E_2 50 group to 20% in the 50/400 group, and vaginitis ranged from 9% in the 50/140 group to 13% in the $E_2$50 group and the 50/250 group. Under Body as a Whole, headache ranged from 21% of patients in the $E_2$50 group to 25% of patients in the 50/140 group, pain ranged from 13% of patients in the $E_2$50 group to 19% in the 50/140 group, Abdominal pain ranged from 12% in the 50/140 and 50/400 groups to 16% in the E_2 50 group, asthenia ranged from 10% in the 50/140 group to 13% in the 50/250 group, and back pain ranged from 13% in the E_2 50 group to 20% in the 50/400 group. Under respiratory system, rhinitis ranged from 17% in the $E_2$50 group to 20% in the 50/400 group, and sinusitis ranged from 10% in the 50/140 and 50/400 groups to 12% in the $E_2$50 and 50/250 groups. Application site reactions ranged from 17% in the $E_2$50 group to 22% in the 50/400 group.

Overall, almost all systemic adverse experiences increased in these studies when compared to the 3-month vasomotor studies. It is clear that a significant number of patients will have some type of adverse reaction with patches. The longer the wear period, the greater the incidence of AEs. Breast pain, dysmenorrhea, menstrual disorder (bleeding), application site reactions and headache are the significant AEs most likely to cause discontinuation of the use of patches.

Laboratory Findings, Vital signs

No clinical vital signs abnormalities, which included supine blood pressure and heart rate were identified in studies 303-304. Weight change was minimal, mean change ranged from 0.33kg in the placebo group to 0.83 kg in the 50/400 group at week 12. Based on available laboratory data, there are no clinically significant findings related to serum chemistries, hematology and urinalysis noted in any of the treatment groups.

Mammography and Pap smear results will be considered separately because fairly high percentages of baseline results were abnormal. For baseline mammography, 14% to 21% of patients in any group were reported to have an abnormal baseline mammography. Several patients had repeat mammograms or additional clinical or laboratory evaluations (i.e., biopsies or ultrasounds); results showed the abnormalities to be clinically acceptable and patients were allowed to participate in the studies. Pap smear abnormalities were noted in 11% to 19% of patients in any group at baseline. All patients had Pap smears findings which were judged to be clinically acceptable by the investigator for study entry. However, patient _ in the 50/140 group, probably should not have been entered into the study because of high grade cervical intraepithelial neoplasia (or severe dysplasia).

The sponsor reported one year comparative data on lipoproteins. Overall, it can be interpreted that no clinically significant benefit was derived from treatment with the E_2 /NETA groups when compared to the estrogen only arm. Although total cholesterol and triglycerides were reported to be statistically significantly better in the E_2/NETA groups, the negative effects of E2/NETA upon HDL cholesterol do not compensate for changes in total cholesterol and triglycerides. This is substantiated by slightly decreased or unchanged ratios of both TC/HDL-C and LDL-HDL-C at one year.

SAFETY UPDATE

All studies were completed between May and July of 1996. In a letter dated December 4,1997, the sponsor states No additional patients had been treated with study drug since the cut-off date of August 12, 1996. On July 16, 1998, the sponsor submitted an additional safety update of a comparative bioavailability study of 76 patients, of which 38 were treated with CombiPatch and 38 were treated with Estragest. No significant or additional AEs were noted in this study which had not been seen in the four U.S. studies. Two additional studies were started in Japan in September 1996 for which one serious ADR has been reported. This involved a patient in study 205 who developed a cerebral infarct while receiving treatment drug.

11 Labeling Review

In general, the proposed labeling submitted corresponds to the August 1992 revision of the "Labeling Guidance for Estrogen Drug Products." Draft labeling reviewed from the sponsor is dated June 23, 1998. The Physician's label will be reviewed first.

Under Description:
This section appears appropriate, the chemist may respond in more detail.

Under Clinical Pharmacology:
This section needs to be substantially rewritten to include pharmacological information only. The biopharmaceutical review has been completed and will conform to the draft guidance which has been recently formulated by the division of biopharmaceutics. Starting on page 4 of 21, the last paragraph, and proceeding to page 10, data should be revised and either deleted or transferred to another section.

a. On page 4, the paragraph which discusses should be deleted.
b. A special populations section and a pediatric section should be placed after in the pharmacology section.
c. All data relating to should be removed and placed in a newly created clinical studies section. This section should be placed immediately *prior* to the Indications section.
d. The two tables entitled should be revised by deleting

e. The two tables entitled
should be revised. The row referring to should be deleted and only identified. In study, 202, first table, third row in column under 0.05/0.25 mg/day, an additional pregnancy was identified, therefore, the percent is 1.03 (1/97). Additionally, the total number of hyperplasia cases in the Vivelle column should be The number of cases in the second table are correct, after deleting

f. The sponsor can elect to include or delete the confusing tables on lipoprotein effects. If these tables are maintained, the following statement must be made:

If these table are maintained, the should be deleted from each column.

g. Under the Indications and Usage section, the sentence after , which is

should be deleted.

h. Under Contraindications, no changes

i. Under Warnings, the following changes should be made:
Induction of Malignant Neoplasm:
Endometrial Cancer: This paragraph should be modified to the following:

In the next paragraph which begins The word should be changed to
Under Visual Abnormalities, this paragraph should be changed to the following,

Under Cardiovascular Effects, #2 the second sentence should be revised to

. The third sentence should be deleted.
Under Nursing Mothers, the sponsor's paragraph should be replaced with the following

Under Dosage and Administration, the study site of administration is the lower abdomen. The buttock site $AUC_{(0\text{-}132)}$ is *not* bioequivalent to the abdomen for both norethindrone and estradiol. Additionally, as compared to other estrogen-only patches, the buttock usually releases more estradiol than the abdomen, however, with the combination patch this is reversed and the reasons for this reversal are not clear. Additionally, it is strongly recommended that the initial dose of the patch should be the 50/140 dose, not the 50/250 dose. The sponsor's studies show women generally had adequate relief of VMS and endometrial protection, experienced less bleeding, had a higher rate of amenorrhea, and less breast pain with the 50/140 dose compared to the 50/250 dose. If a higher dose is required based upon the individual patient's evaluation, the physician can titrate upward to the 50/250 dose. This maintains the premise, that the lowest effective dose

should always be used in hormone replacement therapy. Additionally, in this section under Application of the System, site selection, reference to the should be deleted.

Patient Package Information
Under reference to the should be deleted.
Under the last paragraph relating to breastfeeding should be deleted.

12 Conclusions

The sponsor had demonstrated through four adequate and well controlled clinical trials, the safety and effectiveness of CombiPatch (Aliatis) or (estradiol and norethindrone acetate transdermal system) in reducing symptoms associated with the menopause and the reduction of endometrial hyperplasia when compared to estrogen alone.

13 Recommendation

Approval of this application upon completion of labeling revision and concurrence from all disciplines once reviews are completed.

/S/

Phill H. Price, M.D.
July 14, 1998 and
July 30, 1998

I concur - /S/