CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-907

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 20-907

Trade Name:ACTIVELLE

Generic Name:(estradiol/norethindrone acetate tablets)

Sponsor: Novo Nordisk Pharmaceuticals

Approval Date:November 18, 1998

INDICATION: Provides for the use of Activelle (estradiol/norethindrone acetate tablets) for the treatment of moderate to severe vasomotor symptoms associated with the menopause and in the treatment of vulvar and vaginal atrophy in women with an intact uterus.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-907

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-907

Novo Nordisk Pharmaceuticals
Attention: MaryAnne McElligott, Ph.D.
Regulatory Affairs
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

NOV 18 1998

Dear Dr. McElligott:

Please refer to your new drug application (NDA) dated November 7, 1997, received November 19, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Activelle™ (estradiol/norethindrone acetate tablets).

We acknowledge receipt of your submissions dated December 16, 1997, and January 9, March 18, 19, and 25, July 8, 10, and 22, September 14, October 14 and 28, and November 3, 6 (3), 11, 17 and 18 (2), 1998.

This new drug application provides for the use of Activelle™ (estradiol/norethindrone acetate tablets) for the treatment of moderate to severe vasomotor symptoms associated with the menopause and in the treatment of vulvar and vaginal atrophy in women with an intact uterus.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician and patient labeling dated November 18, 1998, and the draft carton and container labels dated November 6, 1998. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-907." Approval of this submission by the Food and Drug Administration is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated November 6, 1998.

Submit protocols, data, and final reports related to this Phase 4 commitment to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of your commitment in the annual report to this NDA. For administrative purposes, all submissions relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitment."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

Florence Houn, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-907

MEDICAL REVIEW(S)

NOV 10 1998

Medical Officer's Summary of NDA 20-907

1. NDA 20-907
M.O. Review: #1

Submission Date: November 12, 1997
Review Completed: November 9, 1998

Drug: Estradiol and Norethindrone acetate tablets

Generic name: 17 beta estradiol and norethindrone acetate, USP

Proposed Trade Name: Activelle

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: Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Pharmacologic Category: Estrogen/Progestin

Proposed Clinical Use: Hormone Replacement Therapy(HRT) In Women with a Uterus

Dosage and Route of Administration: 1 mg Estradiol (E^2) in combination with 0.5 mg Norethindrone acetate(NETA)

NDA Drug Class: 3S

Related Drugs: The only approved oral HRT products are Prempro™ and Premphase™, there is one transdermal HRT product approved in 1998, Combipatch™

Related Review: Statistical review dated: October 16, 1998
Biopharmaceutics review dated: November 10, 1998

2. Table of Contents:

3. Material Reviewed: Volumes: 1.1, 1.2. 1.23-1.72

4. Chemistry/ Manufacturing Controls: See Chemist review

5. Pharmacology/Toxicology: See Pharmacologist review

6. Clinical Background:

Estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. By direct action, it causes growth and development of the vagina, uterus and fallopian tubes. With other hormones, such as the 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 with associated sleep disturbances and excessive sweating; urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal women.

It has been known for about 20 years that the use of unopposed estrogen replacement therapy in women with an intact uterus has been an intact uterus has been associated with an increased risk of endometrial cancer. Concomitant use of a progestin in a sequential or a continuous manner, i.e., every day, significantly reduces the risk of

endometrial cancer associated with estrogen treatment. Adequate dose and duration of progestin use are important for ensuring endometrial protection.

Activelle™ was developed to provide a fixed therapy for the menopausal women with a uterus who suffer from symptoms of estrogen deficiency and who wish to avoid the monthly bleeding episodes associated with sequential regimens. A continuous combined HRT regimen is characterized by daily concomitant and continuous administration of progestin in combination with estrogen, this does not cause regular monthly withdrawal bleeding, although some bleeding or spotting episodes may occur.

6.1 Relevant human experience

The sponsor has marketed Kliogest®, a continuous combined fixed HRT product containing 2 mg E_2 and 1 mg of NETA, since 1984 and is marketed in most European countries, as well as Australia, New Zealand, and certain countries from Eastern Europe, Asia, Africa, and Central-South America. Prempro® and Premphase®, approved December 1994, are the only approved oral estrogen/progestin combination products in the US and contain various dosages of conjugated estrogens and medroxyprogesterone acetate, in combined and continuous regimens.

6.2 Important information from related INDs

Studies in the US with this product were conducted under IND by the sponsor, Novo-Nordisk.

6.3 Foreign experience

As previously stated, Kliogest® has been marketed in European countries since 1984, and is presently marketed in most of the world. Ongoing clinical trials are being conducted in the US, Norway, Sweden and Japan.

6.4 Human Pharmacology, pharmacokinetics and pharmacodynamics

In postmenopausal women, the principal source of estrogen is in adipose tissue. Estrogens diffuse through cell membranes and bind to and activate the nuclear estrogen receptor, a DNA binding protein which is found in estrogen responsive tissue. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements. The process enhances the transcription of adjacent genes and leads to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens stimulate hepatic synthesis of the renin substrate, angiotensinogen, sex hormone binding globulin (SHBG), corticosteroid-binding globulin (CBG) and certain clotting factors. Estrogens can cause changes in circulating lipids leading to decreased concentrations of low-density lipoprotein cholesterol and increased concentrations of high-density lipoproteins.

Norethindrone acetate (NETA), a synthetic nortestosterone derivative, is one of the potent orally active progestin compounds. Progestin diffuse freely into the cells, where they bind to the progesterone receptors and ultimately influence transcription of a limited set of genes. Progesterone promotes the cell differentiation at the expense of growth, and in turn modifies some of the effects of, and acts mainly on tissues sensitized by, estrogens. In particular, this is evidenced by the transformation of the endometrium from a proliferative to a secretory state. The anti-estrogenic action of progestins is mediated in part by the induction of 17β-hydroxy steroid dehydrogenase, which catalyzes the oxidation of estradiol to the less potent estrone, an estrogen sulfotransferase, which catalyzes the sulfatation and inactivation of estrogens. Most metabolites are excreted as sulphate and glucuronide conjugated in the urine.

Unopposed estrogen administration increases estrogen and progestin receptor concentration in the endometrium. continuous presence of a progestin in the endometrium causes a down-regulation of estrogen and progesterone receptors and thereby endometrial atrophy.

Single dose pharmacokinetic(PK) studies of Activelle showed E_2 reached a peak plasma concentration of approximately pg/ml within hours, while $t_{1/2}$ was about 12-14 hours; plasma concentrations of norethrindrone (NET) was about ng/ml, which was reached hours after dosing. The $t_{1/2}$ of NET was approximately hours. Multiple dose pharmacokinetics showed that levels of E_2, E_1, E_1S, and NET reached steady-state within two weeks and remained constant thereafter following dosing with one tablet of 1 mg E_2 + 0.5 mg NETA once a day. No interaction of NETA on the PK of E_2 was observed and E_2 did not influence the PK of NETA. No effect of age was observed on the level of E_1S when analyzed in women above and below age 65. No significant food effect was observed in the fed and fasting states.

7 Description of Clinical Data Sources

Clinical studies were conducted in the US under IND A supportive phase 3 study was also conducted in Norway. The sponsor conducted 3 primary efficacy studies to investigate two primary endpoints: vasomotor symptoms and estrogen-induced endometrial hyperplasia. Studies KLIM/PD/8US and KLIM/PD/9US were designed to evaluate the effectiveness of 1 mg E_2 + 0.5 mg NETA on the reduction of vasomotor symptoms (VMS) for women with at least 8 hot flushes per day of moderate-to-severe intensity compared to placebo. Study KLIM/PD/1N investigated VMS but patients were required to have only 5 hot flushes per day of mild-moderate-to-severe intensity compared to placebo. This clinical trial will not be reviewed because efficacy data is not clearly supportive of the two required US studies. Study KLIM/PD/7US evaluated the endometrial protective effect of three NETA doses on the incidence of estrogen-induced endometrial hyperplasia during one year, compared to estradiol alone. Four-hundred twenty-five patients were randomized to studies KLIM/PD/US8-9, 119 were randomized to study KLIM/PD/1N, and 1176 were randomized to study KLIM/PD/US7.

8 Clinical Studies

Study KLIM/PD/8/US

8.1.1 Objective/rationale

The primary objective to this study was to evaluate the efficacy and safety of four doses of estradiol 0.25, 0.5, 1.0, and 2.0 mg for relief of vasomotor hot flushes when compared with placebo treatment as assessed by the patients. Secondary objectives were to evaluate the efficacy of the study drugs on other menopausal symptoms as assessed by the patients (menopausal symptoms list) and to evaluate the efficacy of the study drugs based on the investigators' assessment of menopausal symptoms (Greene Climateric scale).

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 two week washout period (8 weeks if previously on HRT) followed by a 3-cycle (12 week) double blind treatment period. Each cycle was designed to be 28 days to correspond to a physiological premenopausal sex hormonal cycle.

8.1.3 Source and number

The study population comprised 333 subjects obtained from the investigators' sites or through local advertising. The planned sample size was 300 subjects; 594 subjects were screened and 333 qualified for randomization.

Inclusion Criteria:

The study inclusion criteria were:

- generally healthy women aged 40 to 60 years;
- complaints of moderate-to-severe flushes as defined in Appendix 1(not shown); subjects should have an average of 8 moderate-to-severe flushes per day, or a minimum of 56 per week, during the 2-week run-in screening period;
- endometrial thickness of less than 5 mm as measured by transvaginal ultrasound (TVS);
- Serum follicle-stimulating hormone (FSH) level $\geq$ 50 mIU/mL and 17-β estradiol (E_2) value $\leq$ 20 pg/mL and $\geq$ 6 months of amenorrhea (excluding any bleeding induced by cyclical progestin treatment, or any other bib0uterine bleeding of known origin);
- subjects with an intact uterus;
- subjects who have had no previous HRT or who are on combined HRT and have completed the present treatment cycle (including a minimum of 10 days of progestin treatment); and
- ability to understand and comply with the protocol requirements and voluntarily provide written informed consent.

Exclusion Criteria:

The study exclusion criteria precluded entry of woman who:

- previous exposure to exogenous sex hormones during the 8 weeks prior to initiation of study treatment. Estrogen alone treatment within the last 6 moths;
- known or suspected pregnancy as confirmed by pregnancy test at the screening and baseline visits;
- known , suspected, or past history of hormone-dependent tumor;
- abnormal genital bleeding of unknown etiology;
- known history of endometrial hyperplasia;
- endometrial thickness of $\geq$ 5mm as measured by transvaginal ultrasonography(TVS);
- history of chronic hepatic or renal disease including presently active gallbladder disease. Clinically significant abnormal liver and renal function test result;
- deep venous thrombosis, thromboembolic disorders, cerebrovascular incidents or past history of these conditions;
- myocardial infarction or ischemic heart disease;
- presence of any endocrine disorder including type I and II diabetes, except for controlled thyroid disease;
- systolic blood pressure (BP) $\geq$ 160 mm Hg and/or diastolic BP $\geq$ 100 mm Hg, treated or untreated;
- known alcohol or drug abuse or heavy smoking, more than 15 cigarettes a day;
- any evidence of pre-malignant changes in pretreatment mammogram or in a mammogram obtained not more than 9 months prior to start of treatment for which result are available;
- obesity, 20% greater than ideal body weight as defined by the Metropolitan Life Insurance Height/Weight tables;
- history of increased frequency or severity of headaches including migraine headaches during previous estrogen use, HRT regimens, or oral contraceptive therapy;
- concomitant use of steroid hormones or drugs known to influence estrogen metabolism, e.g., barbiturates, rifampicin, phenytoin, carbamazepine;
- known or suspected allergy to the study drug;
- any serious disease or a chronic condition that might interfere with study compliance in the opinion of the investigator; and
- use of any type of study drugs during the 30 day prior to the screening visit.

The investigator could withdraw any subject for the following reasons:

- subject requested discontinuation;
- the investigator initiated removal;
- bleeding episodes (requiring sanitary protection) for more than 2 days and/or persistent episodes of spotting. For those subjects removed due to these reasons, endometrial biopsy was performed to rule out development of endometrial hyperplasia or malignancy. When insufficient tissue sample was obtained, a TVS evaluation was performed to confirm lack of endometrial thickening;
- occurrence of intercurrent illness that affected the subject's further participation;
- lack of compliance with the study requirements;
- loss of subject contact;

- concurrent use of any estrogens, progestins, or glucocorticoids not prescribed in the study.

Study Procedures:

Postmenopausal women with a history of moderate-severe vasomotor symptoms (VMS) who gave written consent to participate in the study underwent screening evaluation consisting of the following assessment: medical, gynecological, and drug histories; physical examination, pregnancy test; transvaginal ultrasonography(TVS); vital sign measurement; TVS to assess endometrial thickness; cervical; Papanicolaou smear; mammography (if not done within the last 9 months); laboratory assessments (hematology, blood chemistry, urine analysis); and serum FSH, E_2, estrone (E_1), and estrone sulfate (E_1S) levels. In addition, the following were completed: detailed explanation of the study, voluntary written consent on or before this visit, and dispensing of a diary with instructions regarding the recording of frequency of hot flushes and other menopausal symptoms and bleeding/spotting episodes.

A second visit occurred within 7 days after the subject had completed 2 weeks of the baseline period. The subject's medical file was evaluated to ensure that the baseline results complied with the inclusion criteria. The visit consisted of the following; vital signs measurement; pregnancy test; collection and evaluation of diaries for frequency of hot flushes, bleeding/spotting episodes and other symptoms; recording of any concomitant medications; recording of adverse events/intercurrent illness; administration of the Green Climateric Scale; randomization and dispensing of the study drug and daily diaries.

Visits 3 and 4 (week 4 and 8) occurred within ±3 days of the end of weeks 4 and 8. The following were following at these visits: vital signs measurement; blood collection for measurements of serum FSH, E_2, E_1, and E_1S; collection and evaluation of diaries for frequency of hot flushes, bleeding/spotting episodes, and other symptoms; evaluation of pill intake information; administration of the Greene's Climateric Scale; recording of adverse events/intercurrent illness; recording of concomitant medications; collection of unused study drugs and empty study drug dial packs; and dispensing of study drug and daily diaries.

The final visit took place ±3 days of the end of week 12 during which all remaining diaries and unused or unused study drug dial packs were collected. In addition, the following were done: physical examination including pelvic and breast; endometrial biopsy or TVS if insufficient tissue sample was obtained to confirm lack of endometrial thickening; obtaining specimens for routine laboratory assessments and serum FSH, E_2, E_1, E_1S assessments; vital signs measurements; evaluation of diaries for frequency of hot flushes; bleeding/spotting episodes, and other symptoms; evaluation of pill intake information; collection of study dial packs and used study drugs; administration of the Greene's Climateric Scale; recording of adverse events/intercurrent illnesses; and recording of concomitant medications.

8.1.3.2

Efficacy

The primary endpoint was the weekly number of moderate to severe hot flushes. This is a different endpoint from the sponsor's proposed modified weekly hot flush weighted scale. The sponsor's weekly hot flush weighted score was not acceptable because it was a composite score which incorporated mild symptoms, did not appear to have been validated, and was not readily interpretable for purposes of product labeling. Therefore, the sponsor, per FDA request, submitted a revised primary analysis based on the mean percentage (and mean absolute number) reduction in the weekly frequency of moderate to severe hot flushes. Secondary endpoints were other menopausal symptoms as evaluated by the subjects and the investigator's evaluation base on the Greene's Climateric Scale. Analyses were carried out to test the hypothesis that there were no differences between each of the active treatments groups and placebo. All comparisons were made using a two-sided test at a significance level of 0.05.

For all efficacy variables, analyses were based on an intent-to-treat population. This population included all subjects who received at least one dose of study medication and who have both a baseline and at least one post-baseline value.

Hot flushes were recorded daily by subjects in diaries as a numbered score which increased with severity; none(0) no vasomotor flushes, mild (1) flush without perspiration, which does not interfere with daily activities or performance, moderate (2) hot sensation or flush with perspiration, which interferes with some daily activities at onset of symptoms, or severe flushes (3) hot sensations with perspiration, which stops any present activity at onset of symptoms. Weekly weighted hot flush score was a composite which took into account the weekly number of hot flushes and the severity of each hot flush. The weekly weighted hot flush score was calculated by multiplying the number of mild hot flushes by a factor of one, the number of moderate hot flushes by a factor of two, and the number of severe hot flushes by a factor of three, and then added on a weekly basis. Percent change from baseline for hot flushes weekly weighted score was calculated for each of the 12 weeks of treatment.

The sponsor further stated:

- the change from baseline (week immediately preceding first dose) in weekly weighted hot flush scores (sum of the hot flush score for the week) was analyzed at week 4 by using the last observation carried forward(LOCF). Results of this analysis were considered primary support for efficacy;
- change from baseline in weekly weighted hot flush scores was analyzed at weeks 8 and 12 by using the LOCF. Results from weeks 8 and 12 were considered secondary support for efficacy;
- percent change from baseline in weekly weighted hot flush scores were analyzed by Cochran-Mantel-Haenszel(CMH) test, based on raw or ranked score, adjusting for center effect because the distribution of data was skewed;
- the descriptive statistics and graphical displays by treatment group were provided for weekly number of moderate and severe hot flushes;

- improvements of 50%, 75%, 80%, 85%, 90%,and 95% on weekly weighted hot flush scores from baseline was also calculated for each treatment group;
- additional analyses were done for center effect, age effect, and menopausal symptoms other than hot flushes;
- the Greene's Climateric Scale was the primary secondary efficacy variable. It consist of 21 items each scored as 0, 1, 2, 3, in order of increasing severity. There are two subgroups, psychological symptoms (items 1 to 11), somatic symptoms (items 12-18), and vasomotor symptoms (items 19 and 20); and
- change in mean hormonal levels were summarized over time and mean values were provided for weeks -2, 4, 8, and 12 by treatment group.

Safety:

Safety variables included daily recording of bleeding/spotting, endometrial biopsy, adverse events, clinical laboratory values, vital signs, and gynecological and physical examinations. Most important of the safety variables was the reading of endometrial biopsies and bleeding/spotting episodes. The sponsor described an algorithm for establishing a final diagnosis for each endometrial biopsy. In summarizing this algorithm, when the initial pathologists did not agree, further evaluation was required by a third pathologist who adjudicated differences. Additionally, the histological diagnosis which showed the most estrogenic effect of the three diagnoses was used as the final diagnosis.

8.1.3.3 Statistical plan

A sample size determination was based on the primary efficacy variable, hot flushes. A sample size of 30 subjects per groups with an estimated standard deviation of 20 was more than adequate to detect a decrease in mean weighted hot flush from 20 to 5 with a power of 0.09 at a significance of 0.05.

Power was recalculated based on a between treatment comparison instead of within treatment comparison since the primary objective was to compare the effect of each of the E_2 groups to that of the placebo group. Thus the change from baseline in weekly weighted hot flushes was treated as the response variable. Using 2-sided t-test with α = 0.05 and estimated standard deviation of 75, with sample size equal to 66 per group, the power to detect a treatment group difference (when the population difference is Δ) between the active groups and placebo is 60 patients per treatment group.

8.1.3.4 Results

There were 594 subjects screened and 333 subjects who were randomized into the 5 treatment groups. Sixty-six were randomized into the placebo group and 68, 64, 67, and 68 were randomized into the 0.25 mg, 0.5 mg, 1.0 mg and 2.0 mg groups, respectively. Table 1 from the sponsor shows subject disposition in this study:

Table 1
Disposition of Subjects

	Placebo	0.25 mg	0.5 mg	1.0 mg	2.0 mg	Total
	66	68	64	67	68	333
Completed Study	55 (83%)	59 (87%)	57 (89%)	55 (82%)	54 (79%)	280 (84%)
Did not complete Study						
Adverse Event	5 (8%)	1 (1%)	3 (5%)	6 (9%)	11 (16%)	26 (8%)
Intercurrent Medical Problems	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (<1%)
Noncompliance with protocol	3 (5%)	5 (7%)	2 (3%)	3 (4%)	2 (3%)	15 (5%)
Ineffective therapy	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Other	1(2%)	3 (4%)	2 (3%)	2 (2%)	1 (1%)	9 (3%)
Total Noncompletions	11 (17%)	9 (13%)	7 (11%)	12(18%)	14 (21%)	53 (16%)

Comment: It is very unusual for only two subjects to discontinue in a 12 week VMS study in the placebo group due to ineffective therapy. This suggests a large placebo effect. The 2 mg group had the most discontinuations due to an adverse event, with 8/11 women discontinuing due to bleeding. Surprisingly, 3/5 women discontinued due to bleeding in the placebo group.

A total of 12 (3.6%) of patients in the ITT population were excluded from the efficacy analyses due to major deviations from the protocol. Review of sponsors' table 3 (not reproduced) showed no centers with more than one subject excluded due to protocol violations and randomized groups were fairly evenly distributed. The primary reasons for exclusion were 4 hormonal violations (E_2 or FSH) and 3 subjects with weight > 20% over allowable weight. One subject was excluded with for than the required number of VMS.

The treatment groups were comparable with respect to age, height weight, time since last menses and weekly rate of moderate to severe VMS. The majority of patients were white (> 90%), with 14 African-American subjects, 11 Hispanic subjects, 5 Asian-Pacific subjects and 1 other.

Baseline menopausal characteristics, on average, showed women in the study to be menopausal from 2.5 years in the 0.25 mg group up to 3.5 years in the 0.5 mg group.

Two hundred fifty-seven subjects (77%) took concomitant medications during study treatment. The most frequent concomitant medications were aspirin for headache and pain (57 subjects), acetaminophen for headache, aches, and cramps (57 subjects), and ibuprofen for headache and pain (53 subjects).

Prior to reviewing the primary efficacy data for study KLIM/PD/8US, it is important to report a telecon between the sponsor and HFD-580. At this telecon the sponsor was told this NDA could be filed provided the primary efficacy analyses were revised. The sponsor

had previously analyzed their primary endpoint of VMS studies as the percent change in "hot flush weekly weighted scores" (HFWWS), which is a composite score that takes into account both the weekly number of hot flushes and the severity of each hot flush (mild, moderate and severe). This scoring system is not acceptable as the basis of a primary endpoint because it incorporates mild symptoms, does not appear to have been validated, and is not readily interpretable for purposes of product labeling. Therefore, the sponsor was told to submit a revised primary analysis based on the mean percentage (and mean absolute number) reduction in the weekly frequency of moderate to severe hot flushes. All reviewed data will therefore reflect absolute mean and percent mean reduction in VMS. The sponsor subsequently complied with this, although some referenced data may refer to HFWWS

The following table shows the primary efficacy variable, mean change in the number of moderate to severe hot flushes per week with the Last Observation Carried Forward (LOCF)- ITT Population (modified from sponsor's table 1.1a):

Table 2
Change In Mean Number of Moderate and Severe Hot Flushes Per Week
Last Observation Carried Forward (LOCF) - ITT Population

	Placebo N = 64	0.25 mg E_2 N = 66	0.50 mg E_2 N = 61	1 mg E_2 N =65	2 mg E_2 N = 68
Baseline	72.0	74.4	73.4	69.6	70.1
Baseline-week 4 Mean(SE) P-Value (vs. Placebo)	39.7 - 32.3(28.9	37.1 -37.3(27.6) 0.397	32.5 -40.9(30.9 0.122	22.9 -46.7(29.8 0.005	16.4 -53.7(22.9 0.000
Baseline -Week 8 Mean(SE) P-Value (vs. Placebo	32.1 -39.9(29.1	26.9 -47.5(26.0) 0.163	18.5 -54.8(25.7 0.004	14.6 -55.0(22.8 0.002	7.5 -62.6(20.4 0.000
Baseline-Week 12 Mean (SE) P-Value (vs.Placebo	29.7 -42.3(30.3)	25.6 -48.7(25.8) 0.242	16.0 -57.3(27.8 0.007	9.1 -60.5(22.0 0.000	5.6 -64.5(20.7 0.000

Note at week 4, no significant decreases were observed in the 0.25 mg and the 0.50 mg doses compared to placebo. At weeks 8 and 12, the reductions in hot flushes in the 0.5mg, 1 mg, and 2 mg were significantly different from placebo. Note the high placebo effect achieved in this study and that placebo continued to decrease hot flushes throughout this study.

Additional review of sponsors' tables 1.2, 1.2a, and 1.3 (not reproduced) which evaluated percent change with and without the LOCF, and the mean number of moderate to severe VMS as opposed to absolute changes in VMS, revealed almost identical results to table 2.

The sponsors' primary secondary variable was the Greene's Climateric Scale. This scale incorporates a vasomotor component and psychological somatic symptoms. The vasomotor component of Greene's scale closely approximates results seen in table 2 for weeks 4, 8, and 12. Psychological symptoms for the 1 mg and 2 mg dose groups reached statistical significance compared to placebo only at week 4 for the 1 mg and at week 8 for the 2 mg. For somatic symptoms, small decreases were observed in the 1 mg

and 2 mg groups at weeks 4 and 12, but no significant differences compared to placebo were observed in any groups at any point in time.

Following the screening visit, serum E_2, E_1, and E_1S mean values increased with each increased dose of E_2 indicating a dose response effect. All E_2 mean values at weeks 4, 8, and 12 exceeded the baseline 20 pg/mL. FSH levels tended to fall in a dose response manner, with the highest levels in the placebo group (80-81 mIU/mL and the lowest levels in the E_2 1 mg and 2 mg groups (56-58 and 37-40 mIU/mL, respectively).

Safety

Three hundred-thirty three subjects (66 placebo group, 68 in the 0.25 E_2 group, 64 in the 0.50 E_2 group, 67 in the E_2 1 mg group, and 66 in the E_2 2 mg group) were evaluated for safety. All subjects who were randomized to the double-blind treatment (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. Each subject was counted only once in the incidence count for that preferred term.

The incidence of treatment-emergent adverse events (TEAEs) were similar for active (68%) compared to placebo (67%). The percentage of subjects reporting TEAEs in the 0.25, 0.50, and 1 mg groups were similar to placebo(60% to 67%), while a higher number of subjects reporting TEAEs was observed in the 2 mg group(79%). The reproductive system, body as a whole, CNS and peripheral , respiratory system and gastrointestinal system were the primary systems with > 10% of TEAEs while the musculoskeletal, psychiatric orders resistance mechanism, skin and appendages, "secondary terms", and urinary system had at least 5% of subjects in one treatment group reported TEAEs.

Table 3 from the sponsor shows TEAEs >5%:

Table 3

Number (%) of Treatment Emergent Adverse Events that Occurred in at Least 5% of Subjects in Any Treatment Group

	Placebo	0.25 mg	0.50 mg	1.0 mg	2.0 mg
	n (%)	n (%)	n (%)	n(%)	n(%)
Total number of TEAEs	44 (67)	41(60)	43(67)	44(66)	54(79)
Postmenopausal bleeding	9(14)	7(10)	4(6)	14(21)	25(37)
Headache	11(17)	12(18)	9(14)	6(9)	8(12)
Breast pain	4(6)	4(6)	2(3)	4(6)	8(12)
Upper respiratory tract infection	6(9)	3(4)	2(3)	7(10)	3(4)
Sinusitis	2(3)	6(9)	6(9)	2(3)	5(7)
Back pain	2(3)	2(3)	2(3)	6(9)	5(7)
Abdominal pain	1(2)	4(6)	2(3)	2(3)	3(4)
Pain	3(5)	0(0)	4(6)	1(1)	2(3)
Nausea	2(3)	0(0)	4(6)	3(4)	2(3)
Diarrhea	4(6)	2(3)	1(2)	1(1)	2(3)
Flatulence	1(2)	0(0)	3(5)	2(3)	3(4)
Dyspepsia	3(5)	1(1)	0(0)	3(4)	0(0)
Depression	1(2)	0(0)	4(6)	0(0)	1(1)
Arthralgia	3(5)	3(4)	0(0)	1(1)	3(4)
Dizziness	0(0)	1(1)	4(6)	1(1)	1(1)
Hypoaesthsia	3(5)	0(0)	0(0)	0(0)	0(0)
Coughing	3(5)	1(1)	0(0)	1(1)	2(3)

The most frequent TEAEs reported were postmenopausal bleeding, headache, and breast pain. These TEAEs appear to increase in a dose response manner, but the incidence rate is not unusually high for an ERT product. Other common TEAEs seen in ERT and HRT studies such as upper respiratory tract infection, sinusitis, back pain, abdominal pain, and pain are seen in comparable rates to other products, depending on amount of estrogen present. Since this is an oral product, symptoms associated with the G. I. tract are not unusually high.

TEAEs of primary interest to ERT products are bleeding/spotting episodes and the potential for the development of endometrial hyperplasia. The number of women reporting bleeding or spotting on at least 1 day during a week period was shown in sponsor's table 14(not reproduced). Bleeding and spotting rates were very similar in the 0.25 mg, 0.5 mg and 1 mg groups compared to placebo(not reproduced). Starting at week 6 the percentage of subjects with increased bleeding or spotting in the 0.1 mg group was at least twice that of the 0.5 mg group and the percentage of bleeding from the 10th week onward was 2x greater in the 2 mg group compared to the 1 mg group. At weeks 11 and 12, the percentage of subject bleeding or spotting was 20% of subjects; the percent of bleeding/spotting was statistically significant different from placebo at p=0.05 level. Bleeding was shown in sponsors' table 13(not reproduced). The number of subjects bleeding in the 0.25 mg, 0.5 mg. and 1.0 mg groups were not significantly different from placebo with the majority of treatment at 12 weeks 1 (< 2%) of subjects.

The percent of bleeding increased to approximately 3(4.9%) after week 5 in the 1 mg group to a high of 8(14%) in the 2 mg group at week 11, which is statistically significant different from placebo at p=0.05 level. In the 2 mg group, weeks 9 through 12, all had between 5 and 8 (8.3%-14%) subjects with bleeding.

The sponsor reported data obtained on 286/333 (85.9%) endometrial biopsies at the end of 12 weeks of treatment. Data reported in tables 9.3a and 15 (not reproduced) are identical. Endometrial biopsy data suggest a strong dose dependent effect upon the endometrium. This is shown by the subject having an increased percentage of atrophic endometrium 32 (56.1%) which decreased with increasing dose of estrogen, with the percent of atrophic endometrium being 29 (50.0%), 25 (48.1%), 12 (20.7%), and 4 (6.6%) in the 0.25mg, 0.50 mg, 1.0 mg and 2.0 mg groups respectively. The estrogenic effect is shown again in the percent of subjects with proliferative endometrium. In the placebo group, 9 (15.8%) of subjects had a proliferative endometrium, while 19 (32.8%), 19 (36.5%), 34 (58.6%), and 44 (72.1%) of subjects had a proliferative endometrium in the 0.25 mg. 0.50 mg, 1.0 mg, and 2.0 mg, respectively. The unopposed estrogen effect is most strikingly demonstrated in the percent of subjects with endometrial hyperplasia. Ten cases of endometrial hyperplasia were reported in this study. One subject was reported to have complex endometrial hyperplasia in the placebo group, 1 subject was reported to have complex hyperplasia with *atypia* in the 0.5 mg group, 1 subject was reported to have simple hyperplasia in the 1.0 mg group, and 7 were reported to have simple hyperplasia in the 2.0 mg group.

Of additional interest is the measurement of endometrial thickness via vaginal ultrasound. Vaginal ultrasound was obtained at the end of the study in women who did not have an endometrial biopsy performed or who had endometrial biopsy attempted but had insufficient tissue for diagnosis. Table 9.3b (not shown) outlined 47 cases where an attempt was made to measure endometrial thickness. Of the 47 cases were ultrasound was performed, 17 had no information or were not done, 24 had the desired endometrial thickness < 5 mm, and of the remaining 6 cases with an endometrial thickness of ≥ 5 mm, 3 were in the 0.5 mg group, 2 were in the 1 mg group, and 1 was present in the 2 mg group.

Comment: There appears to be an estrogen induced dose-response effect on the endometrium in this study. This is demonstrated by increased bleeding and spotting, increased bleeding, decreased atrophic and increased proliferative endometrium, and an increased percentage of diagnosed cases of simple hyperplasia. After the diagnosis of endometrial hyperplasia was made, subjects were managed in a consistent manner either per study protocol or by their private physicians.

There were no deaths reported in this study. Six serious adverse events (SAEs) were reported in this study, 2 in the placebo group(peripheral neuropathy and cerebrovascular accident), two in the 0.5 mg group (complex hyperplasia with atypia and basal cell carcinoma of the right cheek), one in the 1 mg group (cholelithiasis), and 1 in the 2 mg group (cervical carcinoma). Of these SAEs the cases of complex hyperplasia and cholelithiasis were probably drug related.

Important clinical evaluations were as follows: there were no clinically meaningful changes in temperature, pulse rate, and respiratory rate during the screening period and

each treatment period; physical examination and gynecological findings from baseline to the end of this study were characterized as normal.

Important laboratory evaluations were as follows: from screening (week -2) to end of the study, no mean changes in glucose or BUN were found in any of the study groups; statistically significant decreases ($p \leq 0.05$) from screening to end of study were found for cholesterol (placebo, 0.5 mg 1mg, 2 mg) alkaline phosphatase (2 mg), SGOT (0.25 mg, 0.5,mg 1 mg, 2 mg) SGPT (0.25 mg, 0.5mg, 2 mg), LDH (1 mg, 2 mg), GGT (0.25 mg, 0.5 mg, 2 mg) sodium (1mg, 2 mg), creatinine (0.5 mg), uric acid (0.5 mg), total protein (0.25 mg. 0.5 mg, 1 mg, 2 mg), total bilirubin (0.5mg , 1 mg, 2 mg), calcium (0.25 mg, 0.5 mg, 1 mg, 2 mg), phosphorous (0.5 mg, 1mg, 2 mg), and potassium (0.5 mg). Mean triglycerides levels increased significantly in the 2 mg group. Mean values of all parameter remained within normal range at the end of the study. No apparent shifts from screening to the end of the study were found for any parameters in any of the treatments groups. Statistically significant decreases ($p \leq 0.05$) compared with placebo were recorded for alkaline phosphatase (2 mg), SGOT (2 mg), LDH (1, 2 mg), total protein (0.5 mg, 2 mg), total bilirubin (2 mg), calcium 1 mg, 2 mg) and phosphorus (0.25 mg, 0.5 mg, 1, mg 2 mg). Additionally, no statistically significant changes from screening to the end of treatment was observed for urinary pH. Statistically significant ($p \leq 0.05$) decreases from screening to end of study occurred for RBC in all active treatment groups, but not in placebo. No changes from screening to end of study were found in any of the treatments groups for WBC, hemoglobin, or hematocrit.

8.1.5 Reviewer's comments/conclusions of study results

In this randomized, double-blind, placebo-controlled study the 1 mg and 2 mg dosages of estradiol were statistically significantly better at decreasing vasomotor symptoms than placebo. Starting in the fourth treatment week and continuing through the 12th week of treatment, both the frequency and severity of VMS were improved. At week 8 through 12, the 0.5 mg was statistically significant better than placebo, showing later efficacy than the higher dosages. The 0.5 mg dose gradual titration toward efficacy has been previously seen in other estrogen products such as Vivelle™ 0.25 mg and Fempatch ™0.20 mg, showing that some time period needs to elapse before the lower dose becomes efficacious. A Phase 4 study might show efficacy at the lower dose, if the sponsor sought to obtain approval of this lower dose. Safety appears comparable to other estrogen-only products. Common AEs such as breast pain, headache, and postmenopausal bleeding are seen in comparable percentages to subjects treated with other estrogen-only products. The 2 mg dose clearly had more menstrual-induced bleeding than the other three dosages and had a seven-fold increase in induced endometrial hyperplasia compared to the 1 mg dose.

Study KLIM/PD9/USA

8.1.1 Objectives

The primary objective of this study was to evaluate the efficacy and safety of 1.0 mg 17β estradiol and 1 mg estradiol(E_2 + 0.5 mg norethindrone acetate (NETA) treatment for the relief of vasomotor hot flushes when compared with placebo treatment.

8.1.2 Design

This was a randomized, placebo-controlled, double-blind, multicenter parallel group study of 1 mg E_2 and 1 mg E_2 + 0.5 mg NETA for the treatment of vasomotor and other menopausal symptoms. The study consisted of a two week 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 twenty-four subjects were screened in an effort to obtain 33 patients per treatment group. Each center 7(originally 5) was to enroll and randomize approximately 25 patients. Subjects for the study were recruited from women attending each site. Due to slow patient enrollment, one site discontinued and two additional sites were added. The recruitment of subjects was terminated by the sponsor after 92 subjects were enrolled because of a lower than expected number of study discontinuations and the slow rate of subject recruitment.

Inclusion Criteria:

Identical to study KLIM/PD8/USA except for the following

- had not previously used HRT; or was on combined HRT and had completed the last treatment cycle (that included at least 10 days of progestin treatment) at least 8 weeks prior to random assignment to study drug; or had no estrogen only treatment in the 12 weeks prior to random assignment to study drug

Exclusion Criteria:

Identical to study KLIM/PD8/USA except for the following:

- exposed to any exogenous sex steroid during the 8 weeks, or to exogenous estrogen only treatment during the 12 weeks before the start of study treatment; and

- Obesity, defined as body weight greater than 30% of ideal body weight by the Metropolitan Life Insurance Height/Weight tables.

Subjects could be withdrawn from then study for any of the following reasons:

Identical to study KLIM/PD8/USA except for the following:

- occurrence of an adverse event hat was considered by the investigator and/or medical monitor to represent a risk to the subject's health

Study Procedures:

Patients were enrolled in the study if they had not used estrogen medications for at least 12 weeks or estrogen/progestin medications for at least 8 weeks before being randomized to treatment and if they fulfilled the rest of the inclusion/exclusion criteria. Potential study patients who were using estrogen or estrogen/progestin medications were to give their written informed consent to participate in the study before stopping use of these medications. Potential patients for the study were scheduled to return to the clinic for a screening visit(Visit 1) at approximately 4 weeks before being randomized to treatment. Patients who were found eligible for treatment were to return 4 additional visits(Visits 2-5). Visits 2-5 were identical to study KLIM/PD8/USA.

8.1.3.2

The primary efficacy variable was the weekly number of moderate to severe hot flushes. This is different from the sponsor's proposed modified weekly hot flush weighted score. This weekly hot flush weighted score was not acceptable because it was a composite score which incorporated mild symptoms, did not appear to have been validated, and was not readily interpretable for purposes of product labeling. Therefore, the sponsor, per FDA request, submitted a revised primary analysis based on the percentage (and mean absolute number) reduction in the weekly frequency of moderate to severe hot flushes. Secondary endpoints were other menopausal symptoms as evaluated by the subjects and the investigator's evaluation base on the Greene Climateric Scale. Analyses were carried out to test the hypothesis that there was no difference between each of the active treatment groups and placebo. All comparisons were made using two-sided test at a significance level of 0.05.

For all efficacy variables, analyses were based on an intent-to-treat population. This population included all subjects who received at least one dose of study medication and who had both a baseline and at least one post-baseline value. All other descriptive statistical analyses are referred to study KLIM/PD8/USA since they are identical to this study.

Safety variables included daily recording of bleeding/spotting, endometrial biopsy, adverse events, clinical laboratory values, vital signs, and gynecological and physical examinations. Most important of the safety variables was the reading of endometrial biopsies and the number of bleeding/spotting episodes. Specimens were examined with the same algorithm as was used in study KLIM/PD8/USA.

8.1.3.4 Results

There were 224 subjects screened and 92 were randomized into this double-blind, controlled study of 7 centers in the US. Ninety (90%) of patients completed this study. There were 92 subjects randomized, 34 in the placebo group, 29 in the 1 mg E_2 group, and 29 randomized to the 1 mg E_2 0.5 mg NETA group. Table 4 (from the sponsor) shows subject disposition in this study:

Table 4
Subject Disposition

	Placebo	1 mg E_2	1 mg E_2 + 0.5 mg NETA	All Subjects
Treated	34	29	29	92
Completed Study	34	28	28	90
Discontinued from Study				
Adverse event	0	0	0	0
Noncompliance with protocol	0	0	1	1
Protocol violation	0	1	0	1
Evaluable for Efficacy (ITT)	34	29	29	92
Evaluable for Safety	34	29	29	92

Two subjects did not complete the study. Subject (1 mg E_2) was withdrawn from the study by the investigator because she had a pretreatment FSH of < 50 MIU/mL. Subject (1 mg E_2 + 0.5 mg NETA) was withdrawn by the investigator at visit 4 because she did not return for visit 3.

Ten subjects (6 in the 1 mg E_2, 2 placebo and 2 in the 1 mg E_2 +0.5 mg NETA group) did not meet the *study entry criteria* but were included into the study. Of this total, 5 were reported to have < 56 moderate or severe hot flushes during the 2 week before randomization, one subject had no hot flush data recorded, 1 subject failed to take 7 tablets during a cycle, one subject did not have a pre-treatment mammogram, one subject was > 30% over her ideal body weight, and one subject had a pre-treatment FSH < 50mIU/mL.

Baseline demographic showed the majority of subjects were Caucasian (approximately 97%), 2% were Black, and 1% were Asian. Baseline characteristics showed the treatment groups to be comparable for age,

height, and weight. The mean years since last menses ranged from 2.5 years in the 1 mg E_2 group, to 2.9 years in the placebo group and 3.4 years in the 1 mg E_2 + 0.5 mg NETA group. The mean number of moderate to severe hot flushes at baseline was 75 in the 1 mg + 0.5 mg NETA group, 68.1 in the 1 mg E_2 group and 68.6 in the placebo group. All subjects had discontinued use of estrogen/progestin medications for at least 8 weeks and use of estrogen only medications for at least 12 weeks before the start of study drug therapy.

Concomitant medications were used by the majority of subjects during their participation in the study. None of the subjects used medications that were prohibited by the protocol. Review of sponsor's Appendix C-18 showed a significant number of subjects taking anti-arthritic drugs, antibiotics, vitamins, sinus medications, hypothyroid drugs, and anti-depressants.

The following table (sponsor's revised) shows the primary efficacy variable, mean reduction in moderate to severe hot flushes per week with the last observation carried forward (LOCF)—ITT population:

Table 5

Changes in Mean Number of Moderate to Severe Hot Flushes per Week
Last Observation Carried Forward (LOCF) –ITT Population

	Placebo	1.0 mg E_2	1.0 mg E_2 + 0.5 mg NETA
Baseline- Mean(SD)	68.6(8.1)	68.1 (18)	75.4 (36.8)
Baseline - Week 4 Mean (SD) p-Value (vs. Placebo	40.0(31.4) -28.6 (29.5)	21.9 (25.5) -45.4 (30.9) 0.0464	8.6 (17.7) -66.6 (36.9) 0.0001
Baseline-Week 8 Mean(SD) p-Value (vs. Placebo)	32.5 (25.6) -36.8 (21.0)	10.4 (18.5) -56.8 (22.4) 0.0049	2.1 (5.4) -73.4 (34.8) 0.0001
Baseline- Week 12 Mean (SD) p-Value (vs. Placebo)	29.9 (27.7) -38.7	12.2 (20.7) -55.0 (26.2) 0.0247	2.8 (7.6) -72.7(35.3) 0.0001

Note at week 4, the 1.0 mg dose barely achieves statistical significance, while the 1.0 mg E_2 + 0.5 mg NETA is highly significant. At weeks 8 and 12 both doses were significantly different from placebo. Note the high placebo effect achieved in this study and that placebo continued to decrease hot flushes throughout this study. It is very unusual to have only 2 subjects discontinue from a 3-month placebo controlled study.

Additional review of sponsors table 1.4 and 1.5 (not reproduced) which evaluated percent change with and without the LOCF, and the mean number of moderate to severe VMS as opposed to absolute changes in VMS, revealed also most identical results to table 5.

The sponsors' primary secondary efficacy variable was the Greene's Climateric Scale. This scale incorporates a vasomotor component and psychological somatic symptoms component. The vasomotor component of Greene's scale closely approximates week 8 and 12 o the efficacy data. For the psychological/somatic symptoms component (sweating, dizziness, giddiness, palpitations, fatigue, headache, sleeplessness, irritability, feeling of depression, skin crawls), only the mean weekly scores for fatigue, sleeplessness, and sweats showed any appreciable decrease over time. For these 3 symptoms, the magnitude of the decrease from week 0 over time were approximately the same for the two treatment groups, and were greater than the decrease in the placebo group.

Safety

Ninety-two subjects (34 placebo, 29 1 mg E_2, and 29 E_2 + 0.5 mg NETA) were evaluated for safety. All subjects who were randomized to the double-blind treatment (ITT population) were included in the safety analysis.
Adverse experience were classified into a standardized terminology using the COSTART Coding Symbols for Thesaurus of Adverse Reactions Terms. Each subject was counted only once in the incidence count for that preferred term.

The incidence of treatment-emergent adverse events (TEAEs) were reported in 65% of subjects in the placebo group, 41% in the 1 mg E_2 group, and 62% of subjects in the 1 mg E_2 + 0.5 mg NETA group. The following table shows the sponsors' TEAEs greater than 5%:

Table 6

Number (%) of Treatment Emergent Adverse Events That Occurred in at Least 5% of Subjects in Any Treatment Group

Adverse Event	Placebo	1 mg E_2	1 mg E_2 + 0.5 mg NETA
Breast pain	0	0	6(21)
Headache	6(18)	3(10)	5(17)
Nausea	0	0	3(10)
Upper Respiratory tract infection	2(6)	2(7)	3(10)
Post-menopausal bleeding	1(3)	1(3)	3(10)
Sinusitis	0	1(3)	2(7)
Ovarian cyst	0	0	2(7)
Abdominal pain	0	0	2(70
Endometrial disorder	3(9)	0	1(3)
Flatulence	2(6)	0	1(3)
Allergy	2(6)	0	0
Breast disorder	0	2(7)	0

Most adverse events were of mild or moderate severity, five AEs were severe. Severe AEs were reported for subjects in the placebo group. They include single reports of an endometrial disorder, abdominal pain, arthrosis, headache, and insomnia).

TEAEs that were possibly or probably related to the treatment and occurred in at least 5% of subjects in any treatment group were: breast pain was reported in 6(21%) in the 1 mg E_2 + 0.5 mg NETA, 0 (0%) in the placebo and 1 mg E_2 groups respectively; headache was reported 6(18%) in the placebo group and 3(10%) and 3(10%) in the 1 mg E_2 and 1 mgE_2 + NETA groups respectively; postmenopausal bleeding was reported 1(3%) in the placebo group, and 1(3) and 3(10%) in the 1 mg E_2 and 1 mg + NETA group, respectively; nausea was reported in 0 (0%) of subjects in the placebo and 1 mg E_2 groups and 2 (7%) of subjects in the E_2 + NETA group; an ovarian cyst was reported in 0 (0%) of subjects in the placebo and 1 mg E_2 groups, and 2(7%) of subjects in the 1 mg + NETA group; abdominal pain was reported in 0 (0%) of subjects in the placebo and 1 mg E_2 groups and 2(7%) of subjects in the 1 mg E_2 + NETA group; endometrial

disorder was reported in 3(9%) of subjects in the placebo group, 0 (0%) of subjects in the 1 mg E_2 group, and 1(3%) of subjects in the 1 mg E_2 + NETA group; flatulence was reported in 2(6%) of subjects in the placebo group, 0(0%) in the 1 mg E_2 group and 1(3%) of subjects in the 1 mg E_2 + NETA group.

Comment: In this study, AEs most prominent to the 1 mg E_2 + NETA group were primarily related to their higher rate of breast pain, headache and nausea. Headache was comparable for the two treated groups and occurred less than was seen in the placebo group. Overall, there are only minor difference between the treatment groups except for two subjects in the 1 mg E_2 + NETA group who were found to have an ovarian cyst at the end of therapy. Both subjects had been amenorrheic for 7 months or more prior to study entrance.

AEs most pertinent to a combination oral product include bleeding/spotting patterns, the incidence of amenorrhea and the incidence of endometrial hyperplasia. The percentage of women with bleeding and/or spotting in the placebo group increased from 5.8% in cycles 1 and 2 to 17.6% in cycle 3; the percentage of bleeding and/or spotting in the E2 group increased from 10.7% in cycle 1 to 21.4% in cycles 2 and 3; in the 1 mg E_2 + NETA group bleeding decreased from 39.3% in cycle 1 to 32.2% in cycles 2 and 3. Quantitatively at cycle 3, 5(14.7%) of subjects in the placebo group were spotting and 1(2.9%) of subjects were bleeding; in the 1 mg E_2 group 3(10.7%) were spotting and 3(10.7 %) were bleeding; in the 1 mg E_2 + NETA group 5(17.9%) were spotting and 4(14.3%) were bleeding.

Amenorrhea during all three cycles was reported in 79% of subjects in the placebo group, 72% of subjects in the 1 mg E_2 group, and 48% in the 1 mg E_2 NETA group. At least one episode of bleeding or spotting in all three cycles was reported in 3% of subjects in th placebo group, 7% in the 1 mg E_2 group and 24% in the 1 mg E_2+ NETA group.

Comment: Bleeding and/or spotting episodes are consistent with subjects who are receiving ERT/HRT. The percentage of bleeding/or spotting appears higher than expected in the placebo group, the reason for this is not clear. Bleeding trends in these first three cycles suggest that the unopposed estrogen group would continue to have more bleeding while in the combination product bleeding starts to lessen as a more atrophic endometrium is achieved.

Endometrial biopsy results are shown in the following table:

Summary of Final Endometrial Biopsy Results

Table 7

	Placebo	1 mg E_2	1 mg E_2 + 0.5 mg NETA
Treated	34	29	29
Completed	34	28	28
Biopsy performed	30	26	25
Biopsy result (N, (%)			
Normal	29(97%)	24(92%)	25(100%)
Insufficient tissue	4(13%)	2(8%)	4(16%)
Atrophic endometrium	20(67%)	6(23%)	19(76%)
Secretory endometrium	0	1(4%)	1(4%)
Proliferative endometrium	5(17%)	15(58%)	1(4%)
Abnormal	0(0)	1(4%)	0(0%)
Simple hyperplasia without atypia		1(4%)	
Other	1(3%)	1(4%)	0

Note that biopsies were obtained on 88% (81/92) of subjects. Nine subjects had endometrial thickness evaluation and two subjects were study withdrawals. Importantly, 76% of subjects in the E2 + NETA group are atrophic at cycle 3 compared to 23% in the E_2 group and 67% in the placebo group. Also note the 58% incidence of proliferative endometrium in the 1 mg E_2 group compared to 17% for placebo and 4% in the 1 mg E_2 NETA group. The only subject with atypia was in the unopposed estrogen group. Clearly, the estrogen/progestin regimen is producing an endometrium which is unlikely to bleed or induce hyperplasia.

The two primary pathologist were in complete agreement in 72% (58/81) of subjects. In all cases after review by the third pathologist, the most severe reading was transcribed as the final pathological diagnosis.

There were statistically significant (decreases) from the screening visit to the final visit for the following tests: calcium and total protein in the placebo group; calcium, total cholesterol, LDH, phosphorus, potassium, sodium, total bilirubin, total protein and uric acid in the 1 mg E_2 group; and alkaline phosphatase, ALT, AST, BUN, calcium, total cholesterol, phosphorus, potassium, sodium, and total protein in the 1 mg E_2 + NETA group. In the latter group, there was also a small increase in the WBC count. Except for total cholesterol, in all cases, the mean changes were small and not clinically significant. Total cholesterol declined by 6% in the 1 mg E_2 group and by 13% in the 1 mg E_2 + NETA group. There were no significant changes in triglycerides in the any of the treatment groups.

There were no significant changes observed in the mean values of respiratory rate, blood pressure, radial pulse, and weight in any of the treatment groups. Seven subjects (3 placebo, 2 in the 1 mg E_2, and 2 in the 1 mg $_2$ + NETA) had gynecologic examination

findings at the end of the study that were not recorded as being present before the start of the treatment. The most serious of these seven gynecologic findings was a palpable, tender ovarian cyst in one subject in the 1 mg E_2 + NETA group.

8.1.5 Reviewer's comments/conclusions of study results

In this randomized, double-blind, placebo-controlled study, 1 mg of estradiol and 1 mg estradiol + 0.5 mg NETA were shown to be statistically significant better than placebo. Starting at the fourth week and continuing through the 12th week of treatment, both the frequency and severity of VMS were improved. Safety appears comparable to the other continuous marketed oral product, Prempro™. Common AEs such as breast pain, headache, and nausea are seen in comparable percentages to Prempro. Bleeding and spotting do not appear to be a significant problem with this regimen and should improve over the first year as the estrogen/progestin effect becomes dominant on the endometrium. Two ovarian cysts developed in the 1 mg estradiol + 0.5 mg NETA group, this appears to be unusual in a postmenopausal women, unless the subject was perimenopausal at study entrance.

Study KLIM/PD/7USA

8.1.1 Objectives

The primary objective of this study was to determine the lowest effective dose of NETA (0.1 mg, 0.25 mg, or 0.50 mg/day) given in a continuous fashion in combination with 1 mg 17β-estradiol that will substantially reduce the incidence of endometrial hyperplasia when compared to 1 mg 17β-estradiol alone treatment. The secondary objective was to asses endometrial histological changes and spotting/bleeding episodes following 12 months of therapy.

8.1.2 Design

This was a prospective, double-blind, randomized, parallel-group multicenter study designed to evaluate the safety and endometrial protection of oral three doses of NETA (0.1, 0.25, or 0.50 mg/day) in combination with a single oral dose of 1 mg E_2.

Inclusion Criteria:

The inclusion criteria were:

- Generally healthy postmenopausal women aged 45 years or older;
- Minimum of 12 months past natural menopause;
- Serum Estradiol $\leq$ 25 pg/mL;
- Intact uterus; and
- Ability to understand and comply with the protocol requirement and provide voluntary informed consent.

Exclusion Criteria:

Exclusion criteria are identical to Studies KLIM/PD/8/USA and KLIM/PD/9/USA except for the following:

- Exposure to exogenous sex steroid hormones (estrogen + progestin therapy) during the 8 weeks prior to study entry or treatment with estrogen alone 12 weeks prior to study entry;
- Known or suspected endometrial hyperplasia and/or endometrial thickness as determined by pelvic ultrasound ≥ 4mm.
- Any evidence of (pre) malignant changes in qualifying mammogram or in mammogram obtained no more than 6 months prior to start of treatment for which results are available;
- Use of any investigational drug(s) during the 30 days prior to screening visit or during the study period;
- Known smoking habit ≥1 pack per day.

A subject could be removed from the study for any of the following reasons (these 2 reasons are substantially different from studies KLIM/PD/8-USA and KLIM/PD/9/USA):

- Protocol noncompliance or treatment noncompliance (missing scheduled medication for 5 or more consecutive days);
- Severe and/or unexpected bleeding episodes.

Study Procedures:

Healthy postmenopausal women, with an intact uterus, were explained the study protocol and written consent was obtained on or prior to study visit. The initial screening evaluations consisted of: medical, gynecological, and drug use histories, physical examination and gynecological examination including pelvic and breast examinations, measurements of vital signs, weight, pulse, respiration, and blood pressure; and endometrial biopsy (or pelvic ultrasound to evaluate endometrial thickness if biopsy could not be performed or evaluated for any reason [subjects refusal, cervical stenosis, unable to obtain sufficient tissue, etc.]); a cervical Pap smear, mammography, the collection of samples for laboratory assessments (chemistry hematology, urinalysis, pregnancy test); and a blood sample for serum estradiol (E_2).

Visit 2 occurred 4 weeks after the screening visit. Subjects medical records were reviewed to ensure compliance with the inclusion/exclusion criteria. The following procedures and assessments were carried out: measurements of vital signs, weight, pulse, respiration, and blood pressure, blood sample for potential hormone analysis, evaluation of bleeding/spotting, recording of concomitant medication and recording of adverse events/intercurrent experiences.

Visits 3, 4, and 5 were described as "in-treatment visits." These visits took place ± 4 days of the end of study months 3, 6, and 9. The previously described procedures and assessments at visit 2 were repeated.

At visit 6 (month 12) the last study visit occurred ± 4 days of the end of month 12. The following procedures and assessments were carried out: measurements of vital signs, physical examinations including pelvic and manual breast examination, cervical Pap smear, mammography, endometrial biopsy, pelvic ultrasound to evaluate endometrial thickness, evaluation of bleeding/spotting, collection of blood samples for laboratory assessments, a blood serum sample for analysis of estrone sulphate (E_1S), recording of concomitant mediation use (OTC, prescription), recording of adverse experiences/intercurrent experiences, drug accountability, and compliance check.

8.1.3.2

Efficacy

All subjects were required to undergo an endometrial biopsy at both screening and at the final visit (or early termination). The primary efficacy parameter was the assessment of the presence or absence of endometrial hyperplasia as determined by pathologist 1 and pathologist 2 who were blinded to study drug assignment. A third pathologist adjudicated final endometrial classification when endometrial samples were categorized as abnormal by at least one of the two initial pathologists. The definition of endometrial hyperplasia was based on endometrial histology described in Blaustein's Pathology of the Female Genital Tract. The final endometrial diagnosis was based on the worst case evaluation among the three pathologists. In a few cases where the sample was only evaluated by pathologist #1 (due to missing or broken slides during transportation) this classification was considered as final.

Secondary efficacy variables were the endometrial histology at the end of the study (whether tissue was normal, abnormal, or other). The incidence of each histology was calculated based on the total number of biopsies available (observed data) at the end of study (Visit 6 or at study discontinuation) presented for each individual pathologist; endometrial thickness was determined at the end of study by pelvic ultrasound to determine if endometrial thickness was ≤ 4mm or ≥ 4mm; and bleeding and spotting data were recorded daily by each patient by use of an automated subject diary collection system, "interactive voice recognition system" (IVRS) via telephone to report the bleeding data. Women reported 1 of 3 possible daily options: spotting, bleeding, or no spotting/bleeding. Spotting was defined as uterine bleeding that did not require sanitary protection, while bleeding was defined as uterine bleeding that required sanitary protection.

Safety

Safety parameters included: treatment emergent adverse events, serious adverse events and non-serious adverse events. Subjects with abnormal endometrial histology were treated and followed until medically acceptable histology was established. Clinical laboratory variables which were followed included hematology, blood chemistries and urinalysis. Estradiol (E_2) levels were measured at visit 1 and estrone sulfate (E_1 S)was

measured at visit 6. In addition, mammograms were taken at screening and at the end of the study (last visit or study discontinuation).

Significant protocol amendments were:

- requirements for a mammogram were changed from 12 months prior to entry to 6 months prior to entry
- a specific blood sample and assay for measuring estrone sulfate levels was added to visit 6.
- a 8 week washout period for women undergoing HRT prior to study enrollment was clarified to 8 weeks washout for women undergoing opposed estrogen therapy and 12 weeks for women undergoing unopposed estrogen therapy prior to visit 2
- an exclusion criterion was established for endometrial thickness > 4 mm as determined by pelvic ultrasound
- the exclusion criterion was added for women who smoked $\geq$ 1pack of cigarettes daily; and
- a cervical Pap smear was added to visit 6.

8.1.3.3

Sample size calculation was based on the incidence of endometrial hyperplasia. This rate was assumed to be no more than 1% with the combination groups. The sponsor produced a table with a power of 0.80 and a significance level of 0.05 which showed at a 7% hyperplasia rate, 200 subjects would be required. The sponsor decided to include at least "250" subjects in each dose arm in order to ensure that a reduction of at least 6% in at the endometrial hyperplasia rate could be detected between treatment groups. The expected dropout rate for this strategy was 25%.

The Fisher's Exact Test was used to was carried out to test the hypothesis that there was no difference in the incidence rates of endometrial hyperplasia between the 1 mg E_2 group and each of the E_2NETA combination groups.

The agreement between pathologists for both abnormal and normal histologies was evaluated using Kappa statistics. The Kappa scale ranged from "1" for scenarios of total agreement to "0" for scenarios of complete disagreement. Agreement was separately determined between pathologist #1 and pathologists No.'s 2 and 3 and between pathologist #2 and pathologist #3.

8.1.4 Results

Efficacy

There were 1176 subjects randomized into this double-blind, parallel, multicenter, dose-finding controlled study at 40 sites in the USA. Study sites compared the efficacy and safety of 1 mg 17 β estradiol in combination with three doses E_2 /NETA. There were 296 subjects randomized to the E_2 group, 294 randomized to the E_2 /NETA 0.1 mg group, 291 randomized to the E_2/NETA 0.25 mg group, and 295 subjects randomized to the E_2 /NETA 0.5 mg group. Table 8 shows patient disposition in this study:

Table 8
Study Completion Status

	1 mg E_2	E_2/NETA 0.1 mg	E_2/NETA 0.25 mg	E_2/NETA 0.5 mg
Total Treated	296	294	291	295
Completed, N (%)	212 (71.6)	237 (80.6))	242 (83.2)	234 (79.3)
Total Noncompletions, N(%)	84 (28.4)	57 (19.4)	49 (16.8)	61 (20.7)
Did not Complete due to:				
Adverse event	53 (17.9)	29 (9.9)	27 (9.3)	34 (11.5)
Bleeding	31 (10.5)	16 (5.4)	13 (4.5)	5 (1.7)
Other AE	22 (7.4)	13 (4.4)	14 (4.8)	29 (9.8)
Intercurrent Medical Problems	0 (0)	0 (0)	1 (0.3)	3 (1.0)
Non-compliance with protocol	16 (5.4)	20 (6.8)	14 (4.8)	11 (3.7)
Missed > 5 days within one lunar month	12 (4.1)	14 (4.8)	7 (2.4)	6 (2.0)
Other	4 (1.4)	6 (2.0)	7 (2.4)	5 (1.7)
Ineffective therapy	0 (0)	0 (0)	1 (0.3)	0 (0)
Other Reason	15 (5.1)	8 (2.7)	6 (2.1)	13 (4.4)

Approximately 80% of the subjects receiving E_2/NETA combination products completed the study compared to 72% of the subjects receiving unopposed E_2. This difference was primarily due to the difference in the frequency of AEs leading to discontinuation, 18% in the unopposed 1 mg E_2 group compared to 9% to 12% in the E_2/NETA combination groups; bleeding was the primary reason for discontinuation in the unopposed E_2 group (10.5%) and a low of 1.7% bleeding was reported in the E_2/NETA 0.5 mg group.

Baseline demographic characteristics showed the majority of subjects were Caucasian (>94%); the remaining 6% were non-Caucasian comprised of Hispanic, Black, and Asian subjects in a decreasing order. Subjects had an approximate mean age of 56 years and were on average 7 years postmenopausal. At screening a total of 96 subjects, equivalent to 8% of the population studied in this trial, were more than 65 years of age with an even distribution among groups. The treatment groups were comparable in regard to weight mean (68-69 kg), height (162-163 cm^2), time since last menses (6.9 to 7.4 years), and the use of previous ERT/HRT (22% to 27%).

Review of physical examination data revealed 23% to 27% of subjects in different groups to have some baseline abnormalities on examination of the breast. None of these abnormalities were of sufficient reason to exclude subjects from the study. In addition, 193 subjects were also reported to have uterine abnormalities at baseline that did not exclude them from the study and were similarly distributed among the groups.

A normal endometrial biopsy (or if biopsy could not be performed or evaluated an endometrial thickness $\leq$ 4 mm) was required for inclusion into the study. The following table 9 shows the number of women included according to endometrial screening procedures:

Table 9
Subjects Included Into Study Based on Biopsy or Pelvic Ultrasound Evaluation

Treatment Group	1 mg E_2	E_2/NETA 0.1 mg	E_2/NETA 0.25 mg	E_2/NETA 0.5 mg
No. of Subjects	296 n %	294 n %	291 n %	295 n%
Biopsy	263 (89%)	258 (88%)	258 (89%)	264 (89%)
Pelvic Ultrasound	32 (11%)	36 (12%)	33 (11%)	31(11%)

Of note is 11%-12% of subjects did not have an endometrial biopsy at entrance into this study. The primary reasons for non-attainment of an endometrial biopsy were: "unable to obtain", "patient refusal", "cervical stenosis", and "inability to pass the pipelle." Comment: All reasons stated for none obtainment of an endometrial biopsy are consistent with general treatment of the postmenopausal women. An endometrial thickness of $\leq$ 4 mm is consistent with good clinical practice and subjects were therefore allowed entrance into this study. Two subjects did not have a normal endometrial status at baseline. Subject (in the E_2/NETA 0.5 mg group was mistakenly included with a biopsy indicating complex hyperplasia with atypia. Subject in the 1 mg E_2 group was included with an endometrial thickness of > 4 mm.
Based on the drug accountability data, compliance was analyzed during the last 3 cycles for those subjects with biopsy: 84% in the 1 mg E_2 group and 87% to 90% in the E_2 /NETA combinations. It is noted that for the primary efficacy variable, the incidence of hyperplasia at the end of the study, 8 endometrial biopsies were evaluated by 1 pathologist only, because the biopsy slides were either lost or broken in transit between the pathologists. Three slides were in the 1 mg E_2 group, 3 slides were in the E_2/NETA 0.1 mg group and 2 slides were in the E_2/NETA 0.5 mg group.

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

Table 10
Incidence of Endometrial Hyperplasia

	1 mg E_2 n = 247 n (%)	E_2/NETA 0.1 mg n = 249 n (%)	E_2/NETA 0.25 mg n = 251 n (%)	E_2/NETA 0.5 mg n = 241 n (%)
Incidence of Hyperplasia P - value (vs 1 mg E_2)	34 (13.8%)	2 (0.8%) <0.001	1 (0.4%) <0.001	1 (0.4%) <0.001
Histologic Diagnosis				
Simple	28 (11.3)	1 (0.4)	0 (0)	1(0.4)
Complex	4 (1.6)	0 (0)	0 (0)	0 (0)
Simple with atypia	0 (0)	0 (0)	0 (0)	0 (0)
Complex with atypia	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)

The 95% Confidence Intervals (CI) are: 1mg E_2/0.1 mg NETA 0.8% (0.97%,2.8%), 1 mg E_2/0.25 mg NETA 0.4% (.01%,2.3%), and the E_2/0.50 mg NETA 0.4% (0.1%,2.2%). Note the 13.8% hyperplasia rate in the 1 mg E_2 group with the addition of 2 cases of complex hyperplasia with atypia. In addition, two other cases of complex hyperplasia with atypia were reported in the lower potency NETA groups. Also note that 16% (988/1176) of subjects had no final histological diagnosis at the end of the study.

Comment: Complex hyperplasia is a lesion of serious concern, and most pathologist feel complex hyperplasia is the precursor to endometrial carcinoma and should be treated aggressively. With the past statement in mind, this gives a suggestion, that for full endometrial protection, the 0.5 mg NETA dose may be optimal in suppressing hyperplasia even though the hyperplasia rate is < 1% in this study for the 0.1 mg and 0.25 mg doses of NETA. Ninety-five per cent CI was less than 4% in all E_2/NETA combinations.

Further review of the sponsor's histological evaluation in the ITT analysis (sponsor's table 11a) showed the unopposed estrogen group with 55 (18.6%) abnormal biopsies compared to 3 (1%) in the 0.1 mg NETA group, 1 (0.35) in the 0.25 mg NETA group, and 2(0.7%) in the 0.5 mg NETA group. Of the 18.6% abnormal biopsies, 21(7.1%) were reported to be disordered proliferative endometrium. The clinical relevance of disordered proliferative endometrium is that it may be confused with hyperplasia, but is not premalignant. Further support of endometrial suppression is reported in the increased percentages of atrophic endometrium in the 0.5 mg NETA 138(46.8%) compared to 56(18.9%) in the unopposed estrogen group and 68(23.1%) and 128(44.0%) in the 0.1 mg and 0.25 mg NETA groups, respectively.

For the main efficacy variable, the Kappa value, identifying the degree of concordance, for the two principal pathologist, K was 0.36. For the small number (n =97) of slides which were reviewed by the third pathologist, the concordance rate was 0.35 between pathlogist #1 and pathologist #3, and 0.32 between pathologist #2 and pathologist #3.

Of the secondary efficacy variables, the percentage of bleeding and spotting is most important. Sponsor's table 13(not reproduced) showed for the estrogen-only group, in cycle 1 the percent of bleeding was 4.5%; this percentage gradually increased to 30.4% at the end of the study. For the three NETA groups, bleeding was different, that is, at cycle one bleeding/spotting ranged from 23.4% to 28% in the three groups. By the end of this study, starting in cycle 4, bleeding/spotting gradually decreased to 24.3% in the NETA 0.1 group, 19.0% in the NETA 0.25 mg group, and 13.8% in the NETA 0.5 mg group.

The severity of bleeding was different between the groups. Overtime, the severity of bleeding increased in the unopposed estrogen group and gradually decreased in the NETA groups; this pattern began at cycle 4 and was maintained throughout the study.

Another way of defining the number of bleeding days is the average number of day with amenorrhea. As the distribution was skewed, both the mean (and median) for each group was used for comparison among groups. The subjects in the E_2/NETA 0.5 mg group reported a slightly larger median number of amenorrhea days, 310.5 compared to 271 in the 1 mg E_2 group, 299 in the E_2/0.5 NETA group, and 290 days in the E_2/NETA 0.25 group. The mean number of days were 266.1 for the E_2/0.5 mg group, and 258.7, 269.4 and 273.1 days for the estrogen only group, the 0.1 mg NETA group and the 0.25 mg NETA groups, respectively.

Comment: The mean number of amenorrhea days appears to more clinically relevant than the median number of bleeding days. Loosely interpreted, the mean number of amenorrhea days basically says that in all the studied groups, subjects will have 4 in 5 days with no bleeding or spotting occurring over the 12 lunar month study.

Safety:

Only treatment-emergent adverse events (TEAEs), defined as AEs with onset between the first day of treatment up to and including the 14th day after discontinuation of treatment, will be discussed. All TEAEs were summarized by system-organ class and NN-ARD preferred term.

Systemic adverse experiences were reported at least once in 251 (84.8%) of subjects in the 1 mg E_2 group, 238 (81.0%) of subjects in the E_2/NETA 0.1 mg group, 231 (79.7%) in the E2/NETA 0.25 group and 245 (83.1%) in the E_2/NETA 0.5mg group. Overall, approximately 80% of the exposed subjects had at least 1 TEAEs during the trial. The distribution was similar among the four treatment groups.
Sponsor's table 9.1.1 (not reproduced) reported the incidence of systemic adverse reactions $\geq$ 5%. Symptoms related to the Reproductive disorders were reported in 29.6% to 35.5% of the treatment groups, followed by Body as a Whole were 25.2 to 28.4% of subjects in all treatment groups reported an AE. The most common AEs reported in $\geq$ 10% were: breast pain, post-menopausal bleeding, headache, sinusitis and upper respiratory tract infection.

Under Reproductive disorders, breast pain was reported in 30 (10.1%)of subjects in the 1 mg E_2 group, and 34 (11.6%), 55 (18.9%) and 71 (24.1%) of subjects in the 0.1, 0.25, and 0.5 mg E2/NETA groups respectively; postmenopausal bleeding was reported in 45 (15.2%) of the 1 mg E_2 group and 21 (7.1%), 20 (6.9%) and 15 (5.1%) of the 0.1, 0.25, and 0.5 mg E_2/NETA groups respectively; under CNS and Peripheral, headache was reported in 47 (15.9%) of subjects in the 1 mg E_2 group and 36 (12.2%) , 35 (12.0%) and 48 (16.3%) of subjects in the 0.1, 0.25 and 0.5 mg E_2/ NETA groups, respectively; under Gastrointestinal, nausea was reported in 15 (5.1%) of subjects in the 1 mg E_2 group, and in 9 (3.1%), 12 (4.1%), and 10 (3.4%) of subjects in the 0.1, 0.25, and 0.5 mgE_2NETA groups, respectively; under Body as a Whole, Abdominal pain was reported in 23 (7.8%) of subjects in the 1 mg E_2 group and in 13 (4.4%), 16 (5.5%) and 11 (3.7%) of subjects in the 0.1, 0.25, and 0.50 mg E_2/NETA groups, respectively; back pain was reported in 14 (4.4%) of subjects in the 1 mg E_2 group and in 17 (5.8%), 16 (5.5%) and 17 (5.8%) of the 0.1, 0.25, and 0.5 mg E_2/NETA groups, respectively; hot flushes were reported in 15 (5.1%) of subjects in the 1 mg E_2 group, and in 5 (1.7%), 4 (1.4%) and 12 (4.1%) of subjects in the 0.1, 0.25 and 0/5 mg E_2 /NETA groups, respectively; pain was reported in 20 (6.8%) of subjects in the 1 mg E_2 group and in 12 (4.1%), 14 (4.8%0, and 13 (4.4%) of subjects in the 0.1, 0.25 and 0.5 mg E_2/NETA groups, respectively;

Under Psychiatric disorders, insomnia was reported in 11 (3.7%) of subjects in the 1 mg E_2 group and in 7 (2.4%), 6 (2.1%) and 17 (5.8%) of subjects in the 0.1, 0.25, and 0.5 mg E_2/NETA groups; under Resistance Mechanism, infection viral was reported in 17 (5.7%) of subjects in the 1 mg E_2 group, and in 17 (5.7%) of subjects in the 1 mg E_2 group, and in 11 (3.7%), 13 (4.5%) and 11 (3.7%) of subjects in the 0.1, 0.25 and 0.5 mg E_2/NETA groups, respectively; moniliasis genital was reported in 20 (6.8%) of

subjects in the 1 mg E_2 group, and in 10 (3.4%), 8 (2.7%) and 11 (3.7%) of subjects in the 0.1, 0.25, and 0.5 mg E_2/NETA groups, respectively; under Respiratory system, sinusitis was reported in 31 (10.5%) of subjects in the 1 mg E_2 group, and in 21 (7.1%), 24 (8.2%), and 21 (7.15) of subjects in the 0.1, 0.25, and 0.5 mg E_2/NETA groups respectively; upper respiratory tract infection was reported in 44 (14.9%) of subjects in the 1 mg E_2 group, and in 51 (17.3%), 42 (14.4%), and 53 (18.0%) of subjects in the E_2/NETA groups; pharyngitis was reported in 15 (5.1%) of subjects in the 1 mg E_2 group, and in 9 (3.1%), 6 (2.1%), and 5 (1.7%) of subjects in the E_2/NETA groups.

Comment: None of the reported AEs are noted to be at an increased incidence compared to other approved products, either oral or transdermal. Breast pain appears to show a dose-response reaction to increased doses of NETA, this has also been seen with other products. Other AEs do not appear to show any dose-response to increasing NETA doses.

Adverse events resulting in discontinuation from the study were reported in 53 (17.9%) of subjects in the 1 mg E_2 group, in 29 (9.9%) of subjects in the NETA 0.1 group, in 28 (9.6%) of subjects in the NETA 0.25 MG group, and in 36 (12.2%) of subjects in the 0.5 mg NETA group. Most importantly, were symptoms related to the Reproductive tract. Postmenopausal bleeding was reported in 31 (10.5%) of subjects in the 1 mg E_2 group, and in 16 (5.4%), 13 (4.5%) and 5 (1.7%) of subjects in the 0.1, 0.25, and 0.5 mg NETA groups, respectively; breast pain was reported in 5 (1.7%) of subjects in the 1 mg E_2 group, and in 1 (0.3%), 2 (0.7%) and 10 (3.4%) of subjects in the 0.1, 0.25, and 0.5 mg NETA groups. No other organ system reported an incidence of $\geq$ 5% of subjects discontinuing due to a serious AE. Of interest, under vascular disorders, non- CVD, there were 2(0.7%) reported cases of lower leg vascular disease; These 2 reported cases were deep thrombophlebitis in the 0.5 mg NETA group; the third case was reported as CVA in the 0.1 mg NETA dose.

A total of 41 women reported a total of 49 SAEs after exposure to trial drugs. The number of women with SAEs were 7 in the 1 mg E_2 group, 16 in the E_2/NETA 0.1 mg group, 13 in the E_2/NETA 0.25 mg group, and 5 in the E_2/NETA 0.5 mg group. Seven cases of malignant breast neoplasm were reported with approximately equal distribution in the various treatment groups. Other cancer such as basal cell carcinoma and colon carcinoma are not thought to be estrogen/progestin dependent. Six cases of cardiovascular disorders were reported: 2 cases of deep venous thrombophlebitis in the 0.5 mg NETA group, 1 case of CVA in the 0.1 mg NETA group, 1 case of pulmonary embolism in the 0.25 mg NETA group; 1 case of supraventricular tachycardia in the 0.1 mg NETA group, and 1 case of myocardial infarction in the 0.1 mg NETA group

Clinical laboratory data (blood chemistry, hematology and urinalysis) were examined for changes during treatment. In each treatment groups, while statistically significant differences in mean laboratory values were observed from baseline to end of study for some variables, mean changes in safety parameters were <u>not</u> clinically significant. This is summarized in the following paragraphs:.

- In treatments groups, a significant decrease from baseline to the end of the trial was observed for the following variables: alkaline phosphatase, LDL-cholesterol, phosphorus, total protein, ALAT, ASAT, sodium, urea nitrate, calcium, chloride, total cholesterol, and GGT. Glucose was not modified significantly in any of the treatment groups.

- Triglycerides increased significantly in the 1 mg E_2group, did not change significantly in the E_2NETA 0.1 and 0.25 mg groups, but decreased significantly in the E_2/NETA 0.5 mg group. Potassium decreased significantly in each group, except in the E_2/NETA 0.1 mg group, where no significant changes was observed. Uric acid decreased significantly in the E_2/NETA combination groups, while no significant change was observed in the 1 mg E_2group. Total bilirubin decreased significantly only in the E_2/NETA 0.5 mg group. Creatinine decreased significantly only in the 1g E_2group and E_2/NETA 0.25 mg group.

- Mean values were all within normal range for hematology parameters at the end of the trial. Platelets decreased significantly in all treatment groups. Significant decreases in hemoglobin and hematocrit were observed only in the 1 mg E_2 group. Significant decreases in RBC was observed in the 1 mg E_2 and E_2/NETA 0.25 mg groups. Significant increases in WBC were observed in all E_2/NETA combination groups. At the end of the trial, urine pH was within normal range in all groups. A statistically significant but not clinically relevant decrease was observed in the 1 mg E_2 group.

8.1.5 Reviewer's comments/conclusion of study results

In this randomized, double-blind, parallel group multicenter study, three doses of 1 mg E_2/NETA (0.1 mg, 0.25 mg, and 0.5 mg) were compared to a 1 mg estradiol-only arm in a continuous manner. The primary efficacy parameter was the incidence of endometrial hyperplasia produced in the ITT population at the end of 13-28 days treatment cycles. The 1 mg estradiol-only group had a 13.8% incidence of endometrial hyperplasia after one year and the three estrogen-progestin groups had < 1% endometrial hyperplasia ($p < 0.001$). While highly significant, it must be noted that 188 (16%) of subjects could not be included in the ITT population at one year. Breast pain, upper respiratory tract infection, headache, and postmenopausal bleeding were the most frequent TEAEs, which is consistent with other HRT studies. The percentage of breast pain increased with increasing NETA dose, this is also consistent with other HRT studies. Mean and median number of days of amenorrhea were slightly higher in the 0.5 mg NETA group compared to the estrogen-only group. A qualitative assessment of cytological atypia showed the highest incidence of atrophic endometrium and the lowest incidence of proliferative endometrium were reported in the 0.5 mg NETA group. With one case of simple hyperplasia in the 0.5 mg NETA group compared to 1 case of complex hyperplasia in both the 0.1 and 0.25 mg NETA groups, it appears the greater endometrial protection obtained in this study is in the Activelle (E_2/0.5 mg NETA) group. There were 7 cases of breast cancer diagnosed during this one year trial of over 1,000 subjects, the distribution of breast cancer was similar among treatment groups.

9 Overview of Efficacy—Comparative results between studies

The sponsor conducted two randomized, double-blind, placebo-controlled studies (KLIM/PD/8--KLIM/PD/9) comparing four doses of estradiol (0.25 mg, 0.50 mg, 1 mg and 2 mg) against placebo in one study and one dose of 1 mg estradiol alone plus Activelle (1 mg estradiol/NETA 0.5 mg) against placebo in the second study. Both trials were 12-week studies comparing the relief of VMS in subjects with placebo versus various estrogen and estrogen/progestin doses. In study KLIM/PD/9/USA, starting within the first 4 weeks of treatment and continuing through 12 weeks of treatment, both the frequency and severity of moderate to severe VMS were statistically significant improved compared to placebo for the 1 mg dose of estradiol and 1 mg estradiol plus 0.5 mg of NETA. In study KLIM/PD/8, VMS were statistically significantly improved with the 1 mg and 2 mg doses of estradiol; statistically significantly differences were also reported in the 0.5 mg dose at 8 and 12 weeks of treatment. Amenorrhea was reported in 48% of cycles in the Activelle group. The sponsor's primary secondary efficacy variable was the Greene's Climateric scale. Only the vasomotor component of this scale showed improvement of symptomatology, while there were no statistical significant differences of Activelle from placebo for the psychological/somatic symptoms.

The sponsor conducted a randomized, double-blind, estrogen-only arm controlled, 13-cycle (52 week) study in 4 parallel treatment groups. Overall, 1176 subjects were entered into the ITT population. Of this total, 188 (16%) of subjects 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. In this study, there were 34 (13.8%) of subjects in the estrogen-only arm who developed endometrial hyperplasia compared to two (0.8%) in the 0.1 mg NETA group, one (0.4%) in the 0.25 mg NETA group, and one (0.4%) in the Activelle group ($p < 0.001$). Importantly, there was one case of complex hyperplasia with atypia in the 0.1 mg NETA group and the 0.25 mg NETA group, suggesting less suppression of the endometrium than the 0.5 mg NETA dose. Hyperplasia with atypia has the highest propensity toward developing into frank endometrial carcinoma and is more difficult to treat than simple hyperplasia. Less suppression of the endometrium is further supported by the fact that the 0.1 mg and 0.25 mg doses of NETA had higher incidences of proliferative endometrium and lower incidences of atrophic endometrium than the 0.5 mg NETA dose. This strongly supports the sponsor's conclusion that the optimal dose for endometrium suppression and control of unwanted bleeding is the 1 mg E_2/0.5 mg NETA dose(Activelle).

10 Overview of Safety

A total of 429 subjects were randomized in the ITT population in studies KLIM/PD/8 and KLIM/PD/9. Both studies used the COSTART Coding of Symbols for Thesaurus of Adverse Reactions Term. In study KLIM/PD/8, 55 (83%) of placebo subjects completed the study compared to 59 (87%), 57 (89%), 55(82%) and 54(79%) of subjects in the 0.25 mg, 0.5 mg, 1mg, and 2 mg groups, respectively. In study KLIM/PD/9 34/34 (100%) subjects completed the study in the placebo group and 28/29 (97%) in the 1 mg E_2 group and 28/29 in the 1 mg E_2/0.5 mg NETA group completed this study.

Deaths

No deaths were reported during this clinical program.

Significant/Potential Significant Events

In study KLIM/PD/8, six subjects discontinued due to an serious adverse event. Two subjects discontinued in the placebo group (peripheral neuropathy and cerebrovascular accident), two in the 0.5 mg group (complex hyperplasia with atypia and basal cell carcinoma of the right cheek), one in the 1 mg group (cholelithiasis), and 1 in the 2 mg group (cervical carcinoma). Of these serious adverse events, only complex hyperplasia and cholelithiasis are probably drug related. In study KLIM/PD/9 no subject withdrew due to a serious adverse event.

Systemic adverse experiences occurred in 44 67%) of placebo subjects, and 41 (60%), 43 (67%), 44(66%) and 54 (79%) of subjects in the 0.25 mg, 0.5 mg, 1 mg, and 2 mg estradiol groups respectively in study KLIM/PD/8. Postmenopausal bleeding, headache, and breast pain were the most frequent adverse events, these AEs appeared to increase in a dose response manner, but the incidence rate is not high for an ERT product. Other AEs such as upper respiratory tract infection, sinusitis, back pain, abdominal pain, and pain were seen in comparable incidence rates to other products depending upon the amount of estrogen present. In study KLIM/PD/9 systemic adverse reactions were reported 22 (65%) of placebo subjects, 12 (41%) of subjects in the 1 mg E_2 group, and in 18 (62%) of subjects in the 1 mg E_2 plus 0.5 mg NETA group. Breast pain, headache, postmenopausal bleeding are the most frequent AEs, with breast pain being prominent in only the 1 mg E_2/0.5 mg NETA group. Other AEs such as nausea, respiratory tract infection and sinusitis are seen in comparable incidence rates to other products depending upon the amount of estrogen present.

A total of 1176 subjects were randomized to treatment groups in study KLIM/PD/7. Systemic adverse events occurred in 212 (71.6%) of subjects in the 1 mg E_2 group, 237 (80.6%) of subjects in the E_2/ 0.1 NETA group, 242 (83.2%) of subjects in the E_2/0.25 mg NETA group, and 234 (79.3%) of subjects in the E_2/0.5 mg NETA group. The most frequent AE leading to withdrawal was post-menopausal bleeding, with the highest percentage in the E_2 only arm; breast pain was the most prominent reason for withdrawal in the E_2/0.5 mg group. There were 7 cases of malignant breast neoplasm reported equally distributed among treatment groups; there were 2 cases of deep venous thrombosis in the Activelle group.

Overall, almost all systemic adverse experiences increased over time in the one year study when compared to the 3-month VMS trials. Breast pain, postmenopausal bleeding, and headache are the most likely AEs to cause discontinuation from any of the treatment groups.

Laboratory Findings, Vital signs

There were no clinically meaningful changes in temperature, pulse rate, respiratory rate, and supine blood pressure in any of the studies. Significant laboratory evaluations changes were not reported in the two three-months studies. There were statistically significant differences reported in various treatment groups of laboratory data such as total cholesterol, calcium, total protein, etc., but these changes were not clinically meaningful in the one year study. The sponsor chose to included data on lipoproteins and insulin sensitivity in two other studies conducted in Europe, KLIM/PD/5/S and KLIM/PD/14/D. These data will be reviewed as they relate to labeling claims.

SAFETY UPDATE

The sponsor submitted the safety report for this product on March 18, 1998. The original cut-off date was November 1, 1997; new and follow-up serious adverse event information is provided up to January 1, 1998 for completed studies from the NDA. In addition, the CFRs for the dropouts due to adverse events are included for unblinded studies KLIM/PD/19/USA and KLIM/PD/15/IRL,

Since the cut-off dates for the NDA, two controlled trials (KLIM/PD/19/USA and KLIM/PD/15IRL have been completed and unblinded. The new information presented in this 120-day safety update is primarily base on these two 6-month trials. Since the ISS, new information from an additional 308 subjects included in the two completed unblinded trials is provided, 86 subjects were treated with Activelle. This corresponds to an increase of 16% (308/1954) in the number of subjects in the controlled trials overall and 19% (86/442) in the number of subjects treated with Activelle.

The demographic characteristics of the study populations at the NDA cutoff date, and at the safety data cut off date, are similar with almost all subjects being Caucasian. In the two 6-month trials, 86 subjects received Activelle.

In KLIM/PD/19/USA, 270 subjects were included in the four treatment groups. The rates of discontinuation due to adverse events were as follows: 4% (3/68), 3% (2/67), 9% (6/68), and 7% (5/67) in the placebo, 1 mg E_2, 1 mg E_2 + 0.25 mg NETA, and Activelle groups, respectively. The discontinuation rates in the Activelle combination group were similar or less than those reported in the 12- month trial, KLIM/PD/7/USA (endometrial protection) trials. Among the adverse events frequently reported in the study, , spotting/bleeding accounted for 1 discontinuation in the 1 mg E_2 group, 3 in the 1 mg E_2 + 0.25 mg NETA group, and 1 in the Activelle group. One woman discontinued in the Activelle group due to breast tenderness.

In KLIM/PD/15/IRL, 2 women discontinued from the Activelle group due to and adverse event. One subject discontinued due to breast tenderness, and one subject discontinued due to an unspecified intermittent pain in the pelvis.

Since June 10, 1997 the sponsor was informed of 3 serious adverse events in the reported trials: one case of malignant breast neoplasm in the 1 mg E_2 group in the KLIM/PD/7/USA study, one case of endometrial hyperplasia in the 2 mg E_2 group in the KLIM/PD/8/USA study, and one case of uterovaginal prolapse in the Activelle group in the KLIM/PD/7/USA.

Eight serious adverse events have been reported in trials KLIM/PD/19/USA and KLIM/PD/15/IRS. In the KLIM/PD/19USA trial, 6 serious cases reported: 1 malignant breast neoplasm in the placebo group, one case each of cervical carcinoma, dehydration, an influenza-like syndrome, cellulitis in the 1 mg E_2 + 0.25 mg NETA group, and case of pulmonary carcinoma in the Activelle group. In the KLIM/PD/15/IRS study, one case of UTI and one case of nausea was reported in the 1 mg E_2 group.

There was one case of endometrial hyperplasia with atypia reported in the Activelle group which was reported two months after the end of the trial. Two additional cases of endometrial hyperplasia were reported in the 1 mg E_2 group, and one each in the lower dose NETA groups. Additionally, one case of complex hyperplasia has been reported in study KLIM/PD/8/USA in the 2 mg E_2 group.

Since the cut-off date for the ISS, two new cases of breast cancer have been reported; one in the placebo group (KLIM/PD/19/USA) and one in the 1 mg E_2 group in study KLIM/PD/7/USA. Therefore, a total of 10 cases of breast cancer were reported in all completed and unblinded studies.

There have been no new reports of either surgically confirmed cholelithiasis or cardiovascular and vascular disorders in the completed and unblinded trials. In the remaining on-going trials, one case of surgically confirmed cholelithiasis was reported in the osteoporosis trial.

TEAEs in the KLIM/PD/19/USA trial are very similar to the previously reviewed trials. Breast pain, postmenopausal bleeding, leukorrhea, and upper respiratory tract infections were the most common reported TEAEs. Again, breast pain was reported with increasing dosages of NETA, this is consistent with other trials.

Laboratory test and vital signs finding were consistent with those the three primary studies.

The sponsor presented revised data for endometrial hyperplasia in the KLIM/PD/7/USA trial. For 3 women in the estrogen-only group, the end-of-trial diagnosis was mis-classified, as the end-of-trial diagnosis erroneously was replaced by the diagnosis of the follow-up biopsy taken after treatment with progestogen. The corrected results showed simple hyperplasia without atypia for two women. Therefore, the final incidence of hyperplasia in the estrogen-only group is 36/247(14.6%), with 30 cases of simple hyperplasia, 4 cases of complex hyperplasia, and two cases of complex hyperplasia with atypia.

Special Studies:

The sponsor conducted two special studies which have an impact on proposed labeling. Study KLIM/PD/19/USA was a six-month, double-blind, randomized, placebo controlled study comparing the safety and efficacy of Activelle (1 mg E_2/NETA 0.5 mg), estradiol alone, and placebo in the determination of CVD risk markers in postmenopausal women. Results show the following: Mean total cholesterol decreased significantly from baseline to the end of the trial in the Activelle group compared to placebo. Triglycerides did not change significantly from baseline to the end of the trial in any of the 4 treatment groups, the greatest elevation was in the 1 mg E_2 group. Data on HDL, LDL_1, LDL_2, LDL_3,VLDL, HDL_2, HDL_3, and Lp(a) were considered invalid due to laboratory error with the analyses. Fasting blood sugar levels decreased significantly from baseline to the end of the trial in all treatment groups. Insulin decreased significantly from baseline to the end of the trial in all treatment groups, except the placebo group, which remain unchanged.

Data for the coagulation/fibrinolysis parameters will now be reported. There were no significant changes in factor VII when Activelle is compared to placebo. Mean Factor VII decreased 4.1% compared to a decrease of 13.3% for Activelle. Fibrinogen increased significantly from baseline to the end of the trial with the largest mean increase in the placebo group followed by the Activelle. Antithrombin III decreased significantly in all groups, with a mean percent decrease of -13% in the placebo group and a -20% in the Activelle group. PA1-1 did not change significantly from baseline to the end of the trial in any treatment group except the placebo group, which increased significantly.

In study KLIM/PD/15/IRL the primary efficacy endpoint in this 6-month trial was the evaluation of LDL oxidisability using T_{BARS} (propagation phase and value at 4 hours). Based on the overall evaluation of LDL oxidisability by propagation phase and T_{BARS} at 4 hours, 6 months treatment with 1 mg E_2 did not have any effect on LDL oxidisability in postmenopausal women with Type 2 diabetes. There were no statistically significant differences observed between 1 mg E_2 and Activelle. Lipid, lipoprotein, and carbohydrate metabolism data had not been finalized, but did not appear to be significantly different form data in the previous studies.

9 Labeling

Draft labeling was extensively revised by the review team. Important issues related to the sponsor's proposed draft label, which will have to undergo extensive negotiations, are the following:

10 Conclusion

The sponsor has demonstrated through three adequate and well controlled clinical trials, the safety and effectiveness of Activelle™ in reducing symptoms associated with the menopause and the reduction of endometrial hyperplasia when compared to estrogen alone.

11 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.
11/9/98

Concur- MMann MD
11/10/98

NOV 10 1998

Addendum to Medical Review

NDA 20-907 Amendment

Second Safety Update

The sponsor has submitted a second Safety Update in order to comply with FDA regulations requiring a safety update to be submitted within 120 days of approval of an NDA application. This safety update is dated November 6, and includes any serious adverse event in the sponsor's clinical development program reported after the original 120-day safety update of November 6, 1998.

Clinical trials have now enrolled 3,414 subjects. Of this total, 851 subjects have been exposed to Activelle. Furthermore, 380 subjects have been included in the two ongoing trials which are still blinded.

Safety data is primarily reported from studies 11/USA, 4/F, and 23/D+ NL and are presented according to the treatment group. Three new serious AEs have been reported in 11/USA, including a case of breast cancer in the 1 mg E_2 group. This subject underwent a biopsy which indicated infiltrative and in-situ ductal carcinoma. The patient underwent partial mastectomy and radiation therapy. In the Activelle group, a malignant neoplasm was reported which is unlikely to be related to study drug. In the 4/F study, a second neoplasm was reported to be unlikely to be related to Activelle. A case of myocardial infarction was reported which was unlikely to be related to study drug; and 1 case each of postmenopausal bleeding and cholecystitis are reported as probably related to Activelle.

In the 4F study, a case of myocardial infarction resulting in death was reported which is unlikely to be related to Activelle. A case of cholecystitis was reported and one case of postmenopausal bleeding was reported which is probably related to Activelle. In the 23/D/NL study a case of ovarian cyst was reported as unlikely to be related to Activelle as well as 1 case of abdominal pain which was reported as being unlikely to be related to Activelle.

The sponsor has also submitted initial safety data on two trials which were initiated after the 120-day safety update. These trials are USA/1/USA and AUS/1/AUS. Three serious AEs have been reported in 2 women in this trial. Both cases are blinded One is a ruptured cerebral aneurysm the day after enrollment, and the second case involves postmenopausal bleeding.

In conclusion, the newly reported adverse events do not change the safety profile of Activelle.

/S/

Phill H. Price, M.D.
November 10, 1998