CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-065

MEDICAL REVIEW(S)

OCT 1 4 1999

Medical Officer Review of NDA 21,065: femhrt

Investigational product: Ethinyl estradiol and norethindrone acetate, USP

Proposed Trade Name: FemHRT [redacted] FemHRT 1/5, FemHRT [redacted]

Final Trade Name: femhrt 1/5

Chemical name: Norethindrone acetate [(17-alpha-17-(acetyloxy)-19-norpregn-4-en-20-yn-3-one]
Ethinyl estradiol [(17-alpha)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol]

Pharmacologic category: Progestin/Estrogen

Administration: Oral tablets, once daily

Dosages (3): [redacted]
1.0 mg norethindrone acetate with 5.0 mcg ethinyl estradiol (FemHRT 1/5)
[redacted]

Indications: [redacted] women with an intact uterus
Treatment of vasomotor symptoms associated with menopause
Prevention of osteoporosis

Sponsor: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

CDER stamp date: December 21, 1998

CDER due date: October 17, 1999

MO Review completed: October 8, 1999

Related NDA/INDs: IND [redacted] and [redacted] NDA 17-876 Loestrin™ (NA/EE) for contraception

Related drugs: Approved oral HRT products are Prempro™, [redacted] and Activelle™.
Approved transdermal HRT product is Combipatch™.
Approved for contraception is Loestrin™ (NA/EE)

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PARTIAL LIST OF ABBREVIATIONS

BMD	bone mineral density
CEE	conjugated equine estrogens
CI	confidence interval
CRF	case report form
DB	double-blind
DMEDP	Division of Metabolic and Endocrine Drug Products
DRUDP	Division of Reproductive/Urology Drug Products
DVT	deep vein thrombosis
ETHINYL ESTRADIOL	ethinyl estradiol
ESTROGEN REPLACEMENT THERAPY	estrogen replacement therapy
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
HORMONE REPLACEMENT THERAPY	hormone replacement therapy
ISE	integrated summary of efficacy
ISS	integrated summary of safety
LOCF	last observation carried forward
Mcg	micrograms
Mg	milligrams
MEDICAL OFFICER	medical officer
MOR	medical officer review
MPA	medroxy progesterone acetate
NA	norethindrone acetate
NDA	new drug application
PC	placebo controlled
PK	pharmacokinetics
QOL	Quality of Life
RR	relative risk
SHBG	sex hormone binding globulin
VMS	vasomotor symptoms
VVA	vaginal and vulvar atrophy

1.0 Introduction

Menopause is characterized by an estrogen-deficient state resulting from natural cessation of ovarian function or surgical removal of functioning ovaries. Menopause pathophysiology manifests as a number of clinical signs and symptoms, including loss of bone mineral density (BMD), resulting in risk for osteoporosis; vasomotor symptoms; and genital atrophy. The hot flash, a vasomotor symptom, is the most common menopausal symptom for which postmenopausal women seek treatment. Nearly 80% of women experience hot flashes within the first year of ovarian failure, and many of these women experience hot flashes for at least 5 years. Atrophic changes to the vagina lead to symptoms of vaginal dryness, burning, itching, dyspareunia, discharge, and occasional bleeding or spotting.

Postmenopausal osteoporosis is characterized by decreased BMD, which manifests as microarchitectural deterioration of bone structure resulting in increased bone fragility and an increased risk of fracture. The rate of BMD loss with resultant development of osteoporosis increases in women after menopause. Estrogen replacement therapy (ERT) effectively maintains BMD in postmenopausal women, and may result in increased BMD. In addition, ERT is effective in preventing vasomotor hot flashes and in reversing genital atrophy. ERT reverses atrophic changes in the vulva, vagina, urethra, and trigone of the bladder by helping to restore and maintain normal physiology of the genital-urinary epithelium, as well as cervical and vaginal secretion and vaginal acidity.

However, ERT can induce proliferation of the uterine endometrium, thereby increasing the risk for vaginal bleeding, endometrial hyperplasia, and endometrial adenocarcinoma. Numerous studies have shown that addition of cyclic or continuous progestin to ERT prevents estrogen-induced hyperplasia of the endometrium and lowers the risk of atypical hyperplasia and cancer. Additional studies of combined progestin and estrogen therapy (hormone replacement therapy [HRT]) also suggest that most women receiving HRT attain atrophic endometrial status with amenorrhea after 6 to 12 months of continuous treatment. Therefore, HRT is now accepted as a standard part of treatment to protect against the increased risk of endometrial cancer associated with the use of unopposed estrogen. Adequate dose and duration of progestin use are important for ensuring endometrial protection.

The sponsor's FemHRT is a combination tablet containing norethindrone acetate (NA) and ethinyl estradiol (EE) and was developed for prevention and treatment of hypoestrogenic states in oophorectomized and perimenopausal and postmenopausal women with intact uteri. NA [(17 alpha)-17-(acetyloxy)-19-norpegn-4-en-20-yn-3-one] is a progestational compound, and EE [(17 alpha)-19-norpregna-1,3,5(10)-trien-2oyne-3,17-diol] is an estrogenic compound. FemHRT refers to all NA/EE dosage combinations studied in clinical trials and presented in this New Drug Application (NDA). Adequate dose and duration of progestin use are important for ensuring endometrial protection. The sponsor studied seven different dose combinations; the requested labeled dosages of FemHRT, however, are [redacted] 1/5, and [redacted] mg NA/µg EE. The sponsor asserts that each of these three doses has established efficacy to support the indications of "treatment of vasomotor symptoms" and "prevention of osteoporosis," as well as to support the safety claim of endometrial protection.

2.0 Background

2.1 Regulatory History:

Investigations that supported the submission of this NDA were conducted under IND [redacted] initially submitted on May 24, 1985. The integrated summary of efficacy (ISE) for FemHRT includes data from four clinical studies (376-343, -359, -368, and –390). These studies support the use of FemHRT for the following indications: treatment of moderate to severe menopause-related vasomotor symptoms, [redacted] and prevention of osteoporosis. Seven dose combinations of FemHRT (NA/EE) were investigated in these studies: 0.2/1,

0.5/2.5, 0.5/5, 1/5, 0.5/10, 1/10, and 1/20. Of the 1,837 postmenopausal women who entered these 4 studies, 1006 (55%) received at least 1 dose of FemHRT.

The ISS for FemHRT includes data from 7 clinical pharmacology and 4 clinical studies, with a total of 2025 participants, 1193 of whom received FemHRT. Because of the different lengths of treatment and follow-up, and different reporting methods, some of the safety data from the 4 clinical studies are presented separately; however, data are integrated whenever appropriate.

Parke-Davis representatives met with members of DRUDP and/or DMEDP to discuss the HRT program 12 times between July 12, 1988 and January 14, 1998. A summary of the meetings and the meeting minutes are found in Volume 1.2 of the NDA. In addition, the sponsor presented the Phase 2 study results at the FDA Advisory Meeting held June 21-22, 1991. This meeting discussed the status of unopposed estrogen replacement therapy (ERT) and combined estrogen and progestin hormone replacement therapy (HRT).

For commercial production, a new manufacturing facility needed to be constructed because existing facilities did not have adequate space or equipment for this drug product. Space was obtained in 1994 in an existing [redacted] facility. Construction and qualification was completed in May 1995. Approximately one year later after the manufacture the stability and bio-batches, [redacted] (new owner) informed the company that the facility would be closed in December 1997. A new manufacturing site, Duramed (Cincinnati, Ohio) was located and a facility constructed and qualified by May 1998. Stability batches were produced from June to September 1998 and the NDA was filed in December 1998 with 3-month stability data on the first three stability batches produced at Duramed.

2.2 Clinical Background: see comments in 1.0 Introduction

2.3 International and Marketing Experience:

FemHRT is not marketed in any country. However, "a marketing application for this product was submitted to the [redacted] Medicines Evaluation Board on December 24, 1998. The 1/5 and [redacted] strengths were recommended for approval on August 19, 1999. The College did not recommend granting approval to the [redacted] This product was also submitted to [redacted] on December 18, 1998. Review is ongoing."

Medical officer comment: the sponsor did not state in their response of the Division the exact indications for which the two doses were approved, or why and for what reasons the [redacted] was not approved.

2.4 Human Pharmacology, Pharmacokinetics, and Pharmacodynamics:

In postmenopausal women, the principal source of estrogen is in adipose tissue. Estrogens diffuse through cell membranes, then bind to and activate the nuclear estrogen receptor, a DNA binding protein that 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 eventually 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 (LDL-C) and increased concentrations of high-density lipoproteins (HDL).

Norethindrone acetate (NA), a synthetic nortestosterone derivative, is one of the potent, orally-active progestin compounds. Progestins diffuse freely into cells, where they bind to the progesterone receptors and ultimately influence transcription of a limited set of genes. Progesterone promotes 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 dehydrogenase, which catalyzes the oxidation of estradiol to the less potent estrone, and estrogen sulfatransferase, which catalyzes the sulfatation and inactivation of estrogens. Most metabolites are excreted as sulphates and glucuronides conjugated in the urine.

Unopposed estrogen administration increases estrogen and progestin receptor concentrations in the endometrium. Continuous presence of a progestin in the endometrium causes a down-regulation of estrogen and progesterone receptors, resulting in endometrial atrophy (thinning of the endometrium).

Ethinyl estradiol (EE) is rapidly absorbed, with peak plasma concentrations 1 to 2 hours after administration. It is subject to significant first-pass metabolism, such that the oral bioavailability is ~55% in normal, healthy premenopausal women. Ethinyl estradiol is absorbed more slowly from FemHRT tablets than from solution. The extent of ethinyl estradiol absorption from tablets is slightly lower (14%) than that from solution. Mean $t_{½}$ values are similar for the two treatment groups.

Norethindrone acetate is completely and rapidly deacetylated to norethindrone (N) after oral administration, and the disposition of NA is indistinguishable from that of orally administered N. Thus, the sponsor measured only plasma N concentrations after administration of NA. N and NA are rapidly absorbed, reaching peak plasma levels within 2 hours after dosing. NA is subject to first-pass metabolism resulting in the oral bioavailability of approximately 64%. Norethindrone is also absorbed more slowly from FemHRT tablets than from solution. The mean C_{max} with tablets is 27% lower and occurred 0.7 hours later than the mean value with administration of solution. Mean $t_{½}$ values are similar for the two treatment groups.

The rates of absorption of both EE and NA are decreased in the presence of a high-fat meal. However, the extent of absorption of EE and NA did not decrease with the high-fat meal. All clinical trials of FemHRT tablets were conducted with no restrictions relative to food, and the sponsor recommends that FemHRT can be taken without regard to meals.

Medical officer comment: the steady state levels of FemHRT are not affected by changes in absorption with and without meals, so it may be taken without regard to meals.

3.0 Description of Clinical Data Sources

Four clinical trials were conducted by Parke-Davis and presented in the NDA. FemHRT, at several doses, was studied for:

1) reducing the frequency and intensity of vasomotor symptoms (VMS),
2) protecting the endometrium from unopposed estrogen-induced proliferation and hyperplasia, and
3) preventing osteoporosis, the loss of bone mineral density (BMD).

Of these 4 studies, 3 assessed hot flash frequency (376-343, 376-368, and 376-390), 2 assessed hot flash intensity (376-343 [summarized only] and 376-390), 2 assessed endometrial protection (376-343 and 376-359), and 2 assessed BMD (376-343 and 376-359). The MO reviewer considers trial 368 to be supportive and 390 to be pivotal for the VMS indication. Trial 359, also called the CHART study, is pivotal for endometrial protection (a safety concern and not really an indication), and prevention of osteoporosis.

Each study is summarized individually in the sponsor's ISE and in this review. Primary and secondary efficacy parameters are listed below:

Vasomotor Symptoms:

- Reduction in hot flash frequency and intensity (Primary)
- Hot flash frequency/intensity combination score (Secondary)
- 75% or 100% reduction in hot flash frequency (Secondary)
- Night Sweats (Secondary)

Endometrial Effects:

- Protection of the endometrium from unopposed EE-induced endometrial proliferation and hyperplasia (Primary)
- Vaginal bleeding/spotting (B/S) (Secondary)

Effects on Bone:

- Prevention of loss of BMD (Primary)
- Biochemical markers of bone (serum total alkaline phosphatase, urinary hydroxyproline:creatinine ratio, and urinary calcium) (Secondary)

Additional efficacy parameters:

- Serum lipids
- Vaginal dryness
- Subject's global assessment
- Quality of Life (QOL)

Descriptions of these 4 studies are summarized in Table 3.1, and the number of subjects exposed to study medication by indication is summarized in Table 3.2 on the next page.

3.1 TABLE of Four Clinical Studies

Study Number (dates)	Study Design	Number of Subjects (FemHRT)	Primary Endpoints	Inclusion Criteria	Daily Treatment & Regimen
376-343 (7/85 to 6/91) Supportive*	1-year, active-controlled, partially blinded, parallel-group, pilot dose-response, single center with 4-year, open-label extension	87 (65)	Hot flash frequency, BMD, and endometrial effects	Nonsmoking white and Asian women, naturally or surgically (bilateral oophorectomy) menopausal for ≤5 years, within 10% ideal body weight, no hormone use within 3 months of study entry. Eligibility for open-label extension required completion of the 1-year phase.	NA/EE 0.5/5, 1/5, 0.5/10, 1/10, or 1/20[a] or MPA/CEE 10/0.625. All groups also received Calcium 1000 mg in divided doses.
376-359 (7/89 to 8/93) Pivotal*	2-year, randomized, double-blind, placebo-controlled, parallel-group, 80 centers	1265 (566)	BMD and endometrial effects	Women ≥40 years of age with intact uteri; naturally menopausal (E_2 ≤40 pg/mL and FSH ≥40 mIU/mL), for ≤5 years, atrophic endometria, lumbar spine trabecular BMD 90 to 160 mg/cm^3, within 20% ideal body weight, no hormone or calcitonin use within 6 months of study entry.	NA/EE 0.2/1, 0.5/2.5, 1/5, or 1/10 or EE: 1, 2.5, 5, or 10[b] or Placebo. All groups also received Calcium 1000 mg in divided doses.
376-368 (7/89 to 12/90) Supportive*	16-week, randomized, double-blind, placebo-controlled, parallel-group, 11 centers	219 (176)	Hot flash frequency	Women ≥40 years of age with intact uteri, naturally menopausal (E_2 ≤40 pg/mL and FSH ≥40 mIU/mL) for ≤5 years, averaged ≥20 hot flashes/week during the prior month, no hormone use within 3 months of study entry.	NA/EE 0.2/1, 0.5/2.5, 1/5, or 1/10, or Placebo
376-390 (3/96 to 4/97) Pivotal*	12-week, randomized, double-blind, placebo-controlled, parallel-group, 24 centers	266 (199)	Hot flash frequency and intensity	Women ≥40 years of age with intact uteri, naturally or surgically menopausal for ≤5 years, no hormone use within 8 weeks of study start (4 weeks for transdermal hormone use), ≥56 moderate to severe hot flashes during last week of baseline.	NA/EE 0.5/2.5, 1/5, or 1/10, or Placebo

E = mg Norethindrone acetate/µg Ethinyl estradiol; BMD = Bone mineral density; MPA/CEE = mg Medroxyprogesterone acetate/mg conjugated equine estrogen; Ethinyl estradiol; FSH = Follicle-stimulating hormone.

[a] After one year, subjects in the 1 mg NA/20 µg EE dosage group were randomly reassigned among the 4 remaining NA/EE dosage groups.

[b] The 10 µg EE dosage group was discontinued early due to a rate of endometrial hyperplasia that exceeded the protocol-specified level.

* Medical officer opinion

3.2 TABLE of Number of Subjects Exposed to Treatments by Indication: Four Clinical Studies

Indication Study No.	Placebo[a]	FemHRT (mg NA/µg EE)							FemHRT Combined[b] Subjects	EE (µg)				EE Combined Subjects	MPA/CEE (mg/mg) 10/0.625	TOTAL[c,d]
		0.2/1	0.5/2.5	0.5/5	1/5	0.5/10	1/10	1/20		1	2.5	5	10			
Osteoporosis and Endometrial Protection																
376-343	10	–	–	12	14	13	14	12	65	–	–	–	–	–	12	87
376-359	137	139	136	–	146	–	145	–	566	141	137	141	143	562	–	1265
Total	147	139	136	12	160	13	159	12	631	141	137	141	143	562	12	1352
Hot Flash Frequency and Intensity[e]																
376-343	10	–	–	12	14	13	14	12	65	–	–	–	–	–	12	87
376-368	43	45	41	–	45	–	45	–	176	–	–	–	–	–	–	219
376-390[e]	67	–	67	–	67	–	65	–	199	–	–	–	–	–	–	266
Total	120	45	108	12	126	13	124	12	440	–	–	–	–	–	12	572

EE = Ethinyl estradiol; MPA/CEE = Medroxyprogesterone acetate/Conjugated equine estrogen.

[a] Study 376-343 had calcium-only as control group.

[b] 1006 subjects in Studies 376-343, -359, -368, and -390 received FemHRT (631 in Studies 376-343 and 376-359 + 375 in Studies 376-368 and 376-390).

[c] TOTAL = Sum of subjects in placebo, FemHRT-combined, EE-combined, and MPA/CEE treatment groups.

[d] TOTAL of 1837 subjects were randomized to treatment with placebo, FemHRT, EE, or MPA/CEE (87 in Study 376-343 + 1265 in Study 376-359 + 219 Study 376-368 + 266 in Study 376-390).

[e] Intensity summarized in Study 376-343 (data not presented in ISE) and compared to placebo in Study 376-390.

Shaded areas are the potential to-be-marketed doses, if approved

4.0 Clinical Study 376-343

Medical officer comment: this study was supportive, but not felt to be confirmatory for any efficacy claims or for the safety claim of endometrial hyperplasia protection.

4.1 **Objective:** to study the long-term effects of 4-5 different doses of FemHRT on VMS (frequency of hot flashes), postmenopausal bone loss and endometrial protection; to assess the safety of continuous NA/EE therapy.

4.2 **Study Design:** this was a 1-year, partially blinded, parallel-group, single-center study followed by a 4-year open-label extension study ~~(total of 5 years). Subjects~~ were given the ~~option~~ to receive unblinded calcium-only, or be randomly assigned to MPA/CEE or 1 of 5 dosage combinations of FemHRT (0.5/5, 1/5, 0.5/10, 1/10, or 1/20). Only subjects randomly assigned FemHRT were administered double-blind medication. After completing a 2- to 4-week screening period, qualifying subjects entered the 12-month, partially-blind study period. Subjects remained in their initial treatment groups for the 4-year extension phase, with the exception of subjects in the 1/20 FemHRT dosage group. Results of the 1-year phase indicated that lower dosages of the EE component of FemHRT effectively relieved menopausal symptoms with less vaginal bleeding; therefore, subjects in the 1/20 FemHRT dosage group were re-randomized among the 4 remaining FemHRT dosage groups. All subjects received calcium, 1000 mg, in divided doses.

This study was done in Cleveland, Ohio at the MacDonald Mid-Life Health Center. Enrollment started in July 1985 and the 5-year study was completed by June 1991.

Medical officer comment: the following facts are noteworthy concerning this study:

- **This was not placebo controlled, but did have an unblinded arm with 1000 mg calcium only, and an active control arm with MPA/CEE. Our current recommendations are to have a placebo arm in order to establish efficacy for the highly variable and subjective endpoint of vasomotor symptoms (VMS).**
- **Only hot flash frequency was studied, with no evaluation of hot flash intensity**
- **Mean baseline hot flash frequency varied from a low of 21.5/week in the calcium only group to a high of 64.6/week in the FemHRT 1/20 treatment group; we now recommend a minimum of 50-60 moderate to severe hot flashes per week at baseline.**
- **This study did not include the 0.5/2.5 dose of FemHRT**
- **The primary analyses for vasomotor symptoms were from the Month 4 and Month 12 data; Week 4 and 8 data was collected, but it did not show a statistically significant difference from calcium in the reduction of VMS**
- **This study is considered to be supportive, but not a confirmatory trial to support an indication for vasomotor symptoms, [redacted] or prevention of osteoporosis**

4.3 **Inclusion Criteria:** see the detailed listing found under study 376-390 on page 17-18 of this review; differences from that list are the following:

- All subjects were naturally menopausal
- Women must have stopped taking oral hormones (estrogens and progestins) within at least 3 months before staring the study
- Must be within 10% of ideal body weight
- Must be non-smoking

Exclusion Criteria: subjects with a history of or current breast cancer; diabetes mellitus; uncontrolled hypertension; alcoholism; or thromboembolic, cerebrovascular, liver, gall bladder, or coronary artery disease.

4.4 Population Characteristics and Disposition:

A total of 87 women started this 6-arm study with 73 completing the one-year mark. Sixty-two women entered the 4-year open-label phase of the study, and 48 completed this phase. The 87 postmenopausal women who entered the 1-year study were Caucasian with a mean age of 53 (range 37 to 59 years) and a mean duration of menopause of 32 months (range 12 to 52 months); none had oophorectomies. Ten to 14 women comprised each of 7 treatment groups. A total of 73 completed the 1-year phase; 62 entered and 48 completed the 4-year open-label extension. Of the 14 women who withdrew during the first year, 4 were from the MPA/CEE group, 4 from the 1 mg NA/5 mcg EE group, and 1-2 from the remaining 5 groups. Thirteen withdrawals were due to AEs and 1 was for personal reasons. Of the 14 women who withdrew from the open-label extension, 5 were for AEs, 3 for personal reasons, 2 for lack of compliance, and 4 for other reasons; these were evenly distributed across treatment groups.

4.5 Efficacy Assessments:

Hot Flash Frequency/Intensity: the frequency of hot flashes per week was determined for each subject at each visit (Months 1, 2, 4, 6, and 12). Subjects with monthly hot flash frequencies recorded as seldom, occasional, episodic, or infrequent were valued as 0.25 hot flashes per week. Two hot flashes per month were valued as 0.5 hot flashes per week. Ranked baseline frequencies were compared among treatments at Months 4 and 12 using analysis of variance (ANOVA), with treatment group as the only factor. Hot flash frequencies were ranked within each time interval, and mean hot flash rates were compared among treatment groups using analysis of covariance (ANCOVA), with baseline frequencies (unranked) as the covariate. Planned comparisons included Dunnett's test contrasting each FemHRT dosage group with control (calcium-only).

Endometrial protection: endometrial biopsies were obtained at Months 12, 24, 36, 48, and 60, the results of which were displayed by treatment and year.

Bone Mineral Density: changes in BMD were evaluated by calculating the mean change from baseline at each yearly follow-up visit. Baseline values were compared using ANOVA. Changes from baseline in BMD were compared using ANCOVA with baseline density as the covariate. Ninety-five percent confidence intervals were calculated for the difference in mean change from baseline between the calcium-only treatment group and all hormone treatment groups. Dunnett's test was used to compare each hormone treatment group to the calcium-only treatment group. Mean annual changes from baseline in biochemical markers of bone were summarized and displayed graphically.

4.6 Sponsor Efficacy Results:

Hot flash analysis: these data were performed on 2 groups of patients, those who had hot flashes at baseline (N= 70) and all patients (N= 87). Data from 17 women were excluded due to lack of hot flashes at baseline. At month 12 an additional 10 women, most of whom had withdrawn form the study, were missing time-interval hot flash data. By month 60, data from 37 women were not included due to withdrawal from the study. No data were excluded from the evaluation due to protocol violations.

At baseline, the mean frequency of hot flashes ranged from 21.5 per week in the Calcium-only treatment group to 64.6 per week in the NA/EE 1/20 group. ANCOVA results indicated that treatment differences were statistically significant at both Month 4 and Month 12 ($p= 0.0001$). Each of the 6 hormone treatments was compared with Calcium-only treatment, making a total of 7 arms in the study. The number of women in each arm at baseline ranged from 7 to 14.

Endometrial effects were determined using endometrial biopsy results and frequency of vaginal bleeding/ spotting. Cyclic MPA/CEE therapy induced regular vaginal bleeding whereas continuous NA/EE combination therapy caused dose-related bleeding/spotting in the first 4 months that diminished to minimal

levels for the rest of the study. Most patients in the five NA/EE groups had insufficient tissue or atrophic endometrial biopsies throughout the 5-year study. A total of 61 biopsies were done at the 1-year mark and 53 at the 2-year mark. No NA/EE treated patient developed hyperplasia, and no patient in the study developed endometrial adenocarcinoma during the 5 years. Patients in the Calcium-only arm who underwent biopsy had either insufficient tissue or atrophic endometrium at each yearly visit (total of 18 biopsies over the 5-year follow-up).

Medical officer comment: there are several reasons why this study, by itself, does not confirm the efficacy of FemHRT regarding VMS.

- **This was a very small study with only 87 subjects and an unevenly distributed (not truly randomized) 7 to 14 women per arm at entry**
- **Many of the subjects had fewer than 50 hot flashes per week and 17/87 (20%) had no hot flashes at entry**
  - **Baseline VMS varied greatly between treatment arms**
- **Of the two FemHRT dosage arms seeking approval, only 25 women were studied and they did not show statistically significant reductions in VMS compared to calcium-only until Month 4**
- **The study enrolled only nonsmoking Caucasian and Asian women within 10% of ideal body weight; this is not a representative sample of the target population for this drug.**
- **Due to the small numbers of patients with variable data, this 5-year study also offers little meaningful information regarding the effects of combination NA/EE therapy on lipids and on coronary artery disease**

4.7 Efficacy for Vaginal and Vulvar Atrophy (VVA):

Maturation indices were obtained as well as reports of symptoms associated with vaginal and vulvar atrophy. In addition, based on symptom reports of vaginal dryness, painful intercourse, vaginal itching and painful urination, FemHRT 1/5 and 1/10 reversed symptoms in many of the women presenting at baseline while preventing the development of symptoms in nearly all women asymptomatic at baseline. Results are summarized in the following table, modified by the medical officer to also include data for the calcium-only patients.

Table: Summary of Menopause-Related Symptoms from Baseline to Last Observation in Year 1

SYMPTOMS	*Calcium Only	FemHRT 1/5	FemHRT 1/10
Vaginal Dryness			
Total N at baseline	10	14	14
Symptom at baseline	5	7	9
Relief from Symptom	3 (60%)	7(100%)	6 (67%)
At Risk	5	7	5
Developed Symptom	0	1 (14%)	1 (20%)
Painful Intercourse			
Symptom at baseline	4	6	6
Relief from Symptom	3 (75%)	5 (83%)	5 (83%)
At Risk	6	8	8
Developed Symptom	0	0	0
Vaginal Itching			
Symptom at baseline	0	1	5
Relief from Symptom	0	1 (100%)	3 (60%)
At Risk	10	13	9
Developed Symptom	0	1 (8%)	0
Painful Urination			

SYMPTOMS	*Calcium Only	FemHRT 1/5	FemHRT 1/10
Symptom at baseline	0	0	1
Relief from Symptom	0	0	1 (100%)
At Risk	10	14	13
Developed Symptom	0	0	0

*Column added by medical officer

[redacted]

4.8 Endometrial Protection:

Whenever possible, endometrial biopsies were taken at the end of each year. Most patients in the 5 NA/EE treatment groups had either insufficient tissue or atrophic (normal) tissue throughout the 5-year study. No NA/EE treated women developed endometrial hyperplasia or endometrial adenocarcinoma. There were a total of 50 endometrial biopsies in NA/EE subjects at Year 1, and 45 at Year 2. Of these 95 biopsies, 16 were from FemHRT 1/5 women and 22 were from FemHRT 1/10 women. By Year 5 there were 38 biopsies in NA/EE subjects (6 in the 1/5 group; 10 in the 1/10 group).

Medical officer comment: although there were no endometrial biopsy results showing endometrial hyperplasia in any of the five FemHRT groups over 5 years, the numbers are small (8 to 14 per arm), and the calcium-only group showed the same results. Furthermore, there were no unopposed estrogen arms for comparison.

4.9 Sponsor Safety Analysis:

The most commonly reported symptom in the "placebo" (calcium only) group was constipation. Symptoms in the MPA/CEE group included cramping, hypertension, rashes and hair loss. Among women in the five NA/EE groups combined, stress was the most common complaint followed by rashes, constipation, cramps, hair loss, edema, and hypertention. Adverse events from Years 2.5 to 5, associated with NA/EE treatment were vaginal bleeding in 2 patients and a suspcious Pap smear. One serious AE, deep vein thrombosis (DVT), occurred in 1 patient on NA/EE 1/10 treatment on Day 942. Serious symptoms or AEs, felt by the investigator to be unrelated to NA/EE treatment were breast cancer in 3 patients and tachycardia in one patient..

Medical officer comment: During the first year of the trial and including the first 1½ years of the 4-year open-label extension, systematic recording of AE information was not conducted. Meaningful and accurate AE outcome data is, therefore, not available. AE recording by body systems began in August 1987, so some limited conclusions, as stated above, could be drawn from the study. Another significant factor limiting safety conclusions is the small number of patients in the study and the discrepant sample size between arms. There were no deaths in this 5-year study.

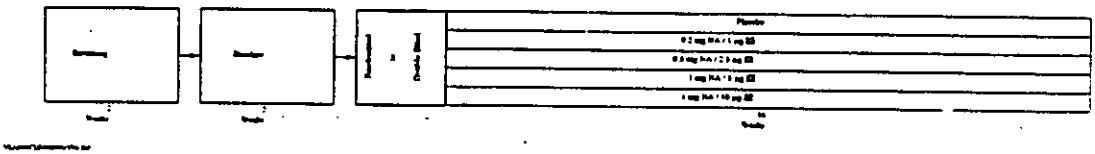
The most remarkable AEs of note were two cases involving thrombophlebitis. A 54 year old subject on FemHRT 1/10 had a documented DVT at 2 years and 7+ months, was hospitalized, treated with IV heparin followed by a tapering schedule of warfarin. The subject had a history of varicose veins; she recovered without sequelae. Another 54 year old subject on NA/EE 1/20 discontinued medication on day 39 due to a superficial thrombophlebitis of the left leg. DVT was ruled out by venogram. These two AEs will be discussed further at the end of this review in the medical officer overview of safety.

5.0 Supportive Clinical Study 376-368

Medical officer comment: this study was supportive, but not felt to be confirmatory for any efficacy claims for treatment of vasomotor symptoms.

5.1 Objective: to compare the efficacy and safety of four dosage combinations of ethinyl estradiol/ norethindrone acetate to placebo for reducing vasomotor symptoms associated with the menopause.

5.2 Study Design: this was a 16-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter study (11 centers). Subjects were randomly assigned to one of 5 treatment groups receiving either placebo or FemHRT (0.2/1, 0.5/2.5, 1/5, or 1/10). After completing a 2-week screening period and a 2-week diary-baseline period, qualifying subjects were entered into a 16-week double-blind period. The study design is shown in the following figure:



Medical officer comment: the following facts are noteworthy concerning this study:

- **Hot flash frequency, not intensity, was assessed; the division requires data for both frequency and intensity of hot flashes to establish efficacy for vasomotor symptoms**
- **Women enrolled in this study had an average of ≥ 20 hot flashes per week in the month prior to enrollment; we recommend a minimal frequency and intensity at baseline of 50-60 moderate to severe hot flashes per week in order to clearly establish efficacy over placebo**

5.3 Inclusion Criteria: same as the criteria listed on page 17 for study 376-390, with the following exceptions:

- Must have stopped taking oral sex hormones within at least 3 months before starting the study;
- Required that women average ≥ 20 hot flashes per week during the month before entering the study, and ≥ 10 hot flashes during the second week of the baseline period;
- Serum FSH value ≥ 40 mIU/mL and serum estradiol value < 40 pg/mL before starting the study.

Exclusion Criteria: subjects with a history of or current breast cancer; diabetes mellitus; uncontrolled hypertension; alcoholism; or thromboembolic, cerebrovascular, liver, gall bladder, or coronary artery disease. Also excluded women with a history of or current renal disease, ovarian cancer, suspicious mammogram or endometrial hyperplasia (assessed by biopsy).

5.4 Population Characteristics and Disposition: a total of 219 women started this 5-arm study with 176 (44/arm) randomized to one of the four FemHRT arms and 43 to the placebo arm. The 219 women were randomly assigned to DB treatment; 31 (14%) patients withdrew before completing the study, leaving 188 who completed the study. Reasons for withdrawal were as follows: seventeen (8%) due to AEs, 4 (2%) due to lack of efficacy, and 10 (5%) for other reasons. The mean age was 51.5 years.

5.5 Efficacy Assessments: Treatment response was evaluated comparing hot flash frequency (hot flashes/week) at baseline and at Week 16 as the primary efficacy parameter. Secondary parameters were percent changes from baseline in hot flash frequency, percentages of patients with clinical success (≥ 75% reduction in VMS), and percentages of patients with elimination (100% reduction) in hot flash frequency.

Statistical Methods: The endpoint analysis of hot flash frequency used ITT data. The baseline was determined from the last 7 available days of data from the 2-week baseline period. Hot flash frequencies at Weeks 8, 12, and 16 were determined using the last 7 available days of data prior to the week being evaluated. The analyses of bleeding/spotting, vaginal dryness, insomnia, and patient global assessment used ITT.

Medical officer comment: further details about the statistical methodology are found in the FDA statistician's review of this NDA.

5.6 Sponsor Efficacy Results: by week 16, mean hot flash frequencies ranged from 11 to 4 hot flashes/week across active treatment groups in an inversely dose-dependent manner, and were all statistically significantly less than the placebo group (26 hot flashes/week). According to the sponsor's analysis, FemHRT treatments effectively reduced hot flash frequency, while treatment with the 1 mcg EE /0.2 NA dosage combination was borderline effective.

Sponsor Table: Hot Flash Response at Week 16 Using Evaluable Data

Parameter	Placebo	FemHRT treatment group (mg NA/ mcg EE)				Overall p-value for treatment effect
		0.2/1	0.5/2.5	1/5	1/10	
# Subjects	36	35	34	36	40	
Baseline hot flashes/week	48	44	42	42	53	
Week 16 hot flashes/week	26	11*	10*	5*	4*	0.0001
% Change from baseline	-47	-78*	-81*	-90*	-94*	0.0001
% Patients with clinical success	33	66*	71*	81*	90*	<0.001
% Patients with 100% elimination	8	20	29	58*	60*	<0.001

* Statistically significantly different from placebo

Medical officer comment: this study was carried out in 1989-90, and the criteria by which efficacy was determined differed from our current recommendations. Some of the important differences between this study and present Division recommendations are outlined below:

- **Primary endpoint was hot flash frequency instead of both frequency and intensity**
- **Used Week 16 data as the primary endpoint instead of Week 4, 8 and 12 data; the Division now likes to see an effect at Week 4 that carries through to Week 12.**
- **Had an average of 46 hot flashes /week at baseline instead of 50-60/week**
- **Used estradiol ≤ 40 pg/mL instead of ≤ 20 pg/mL to confirm "postmenopausal;" therefore, this population may not have met the more strict criteria desired by the Division.**

For the above reasons this study is considered to be supportive, but not pivotal. It was helpful in establishing that the lowest dose studied (1 mcg ethinyl estradiol /0.2 norethindrone acetate) did not appear to be as effective in treating vasomotor symptoms. The sponsor did not include this dose in their subsequent, much larger, pivotal Study 376-390.

In addition to hot flash response, this study examined the occurrence of bleeding/spotting with FemHRT treatments. The percentage of women free of bleeding/spotting increased over time through the end of the study and were greater with lower NA/EE dosage. During weeks 1-4, the percentages of women free of bleeding/spotting ranged from 48% to 89% (high dose to low dose) which increased to range from 67% to 95% during weeks 13-16. The percentages of women free of bleeding were ≥ 70% in all groups at all time points and increased over time (≥ 88% in all treatment groups during weeks 13-16) and with lower dose. As expected, bleeding/spotting were lower when time since menopause (≥12 months) was considered. In the category of subjects with menopause ≥ 12 months, 100% of the women in the placebo and 1/5 treatment groups were free of bleeding during weeks 13-16, while 87% of women in the 2.5/0.50.5/2.5 and 1/10 treatment groups were free of bleeding during weeks 13-16.

5.7 Efficacy for Vaginal and Vulvar Atrophy: Maturation indices were not obtained. Reports of vaginal dryness, a symptom associated with vaginal and vulvar atrophy were analyzed as a secondary efficacy endpoint in a subset of enrolled patients. Only 40% (88/219) of the patients who entered the DB period reported vaginal dryness during baseline. The sponsor performed an endpoint analysis on data from these 88 patients as shown in the table below. The sponsor did not analyze data stratified by patient sexual activity because of the small number of patients providing data.

Sponsor Table: Secondary Efficacy Subset Analysis of the % of Patients with Vaginal Dryness at Baseline Who Continued to Report Vaginal Dryness at Week 16

SUBJECTS (symptomatic)	Placebo	NA/EE Treatment Groups			
		0.2/1	0.5/2.5	1/5	1/10
N at baseline	16	22	20	14	16
N at 16 weeks (%)	12 (75)	10 (45)	4 (20)*	4 (29)*	2 (13)*

*Overall p-value for treatment effect = 0.006
Statistically significantly less than placebo (α = 0/05 with Bonferroni adjustments, one-sided)

[redacted]

5.8 Sponsor Safety Analysis:

All 219 patients who received treatment were included in safety evaluations. The percentages of women experiencing AEs with study drug were similar across all treatment groups in six out of nine body systems. Associated AEs that were experienced by dissimilar percentages of patients between placebo and active drug were those typical of estrogen therapy (bloating, nausea, abdominal pain, and breast pain). These differences were generally most prevalent in the 1/5 and 1/10 treatment groups. The majority of women experiencing AEs considered associated with FemHRT treatment had events of mild or moderate intensity across all treatment groups. By weeks 13 to 16, the percentage of women with NO bleeding/spotting ranged from 95% to 67% with NA/EE treatments and were clinically acceptable. There were no deaths reported during the study.

The sponsor's table below lists those AEs reported by ≥5% of patients in the study. 145 (66%) of the 219 patients experienced at least one AE. Overall, the percentages of patients in the NA/EE treatment groups that reported AEs (63% to 73%) were slightly greater than that of the placebo treatment group (58%). Headache, rhinitis, and myalgia were reported by the largest percentage of FemHRT treated patients; of these, the incidence of myalgia appears to be dose-related.

Adverse Events Reported by ≥5% of Subjects by Body System[a] (Study 376-368)

[Number (%) of Subjects]

BODY SYSTEM Adverse Event	Placebo		FemHRT Treatment Groups, mg NA/μg EE							
			0.2/1[b]		0.5/2.5		1/5		1/10	
	N = 43		N = 45		N = 41		N = 45		N = 45	
BODY AS A WHOLE	14	(32.6)	18	(40.0)	14	(34.1)	13	(28.9	18	(40.0)
Headache	5	(11.6)	8	(17.8)	5	(12.2)	5	(11.1	7	(15.6)
Viral Infection	3	(7.0)	5	(11.1)	4	(9.8)	0	(0.0	3	(6.7)
Pain	1	(2.3)	1	(2.2)	1	(2.4)	3	(6.7	2	(4.4)
Edema – Generalized	1	(2.3)	5	(11.1)	2	(4.9)	3	(6.7	2	(4.4)
DIGESTIVE SYSTEM	5	(11.6)	5	(11.1)	4	(9.8)	8	(17.8	13	(28.9)
Nausea and/or Vomiting	0	(0.0)	1	(2.2)	1	(2.4)	2	(4.4	5	(11.1)
Abdominal Pain	2	(4.7)	1	(2.2)	2	(4.9)	3	(6.7	4	(8.9)
MUSCULOSKELETAL SYSTEM	2	(4.7)	8	(17.8)	6	(14.6)	6	(13.3	7	(15.6)
Myalgia	2	(4.7)	4	(8.9)	3	(7.3)	5	(11.1	7	(15.6)
PSYCHOBIOLOGIC FUNCTION	3	(7.0)	4	(8.9)	5	(12.2)	6	(13.3	6	(13.3)
Nervousness	3	(7.0)	2	(4.4)	2	(4.9)	5	(11.1	4	(8.9)
Depression	0	(0.0)	1	(2.2)	3	(7.3)	2	(4.4	3	(6.7)
RESPIRATORY SYSTEM	12	(27.9)	8	(17.8)	5	(12.2)	8	(17.8	9	(20.0)
Rhinitis	6	(14.0)	5	(11.1)	3	(7.3)	6	(13.3	4	(8.9)
Sinusitis	1	(2.3)	1	(2.2)	0	(0.0)	1	(2.2	3	(6.7)
Upper Respiratory Infection	3	(7.0)	1	(2.2)	1	(2.4)	0	(0.0	0	(0.0)
UROGENITAL SYSTEM	4	(9.3)	7	(15.6)	2	(4.9)	10	(22.2	12	(26.7)
Breast Pain	0	(0.0)	3	(6.7)	1	(2.4)	1	(2.2	6	(13.3)
Vaginal Hemorrhage	1	(2.3)	0	(0.0)	1	(2.4)	5	(11.1	0	(0.0)

[a]The total number of subjects for each body system may be less than the number of subjects with AEs in that body system because a subject may have had more than one AE per body system.

[b]This lowest dose is not one of the FemHRT doses seeking approval.

Medical officer comments:

The above table raises no major safety issues with FemHRT and agrees with the safety profile seen in the slightly larger, better-designed clinical study 376-390. It would appear that nausea and/or vomiting and breast pain are dose-related, being most prevalent in the highest FemHRT dose (1/10). This is not unusual because these symptoms are known to be estrogen related.

There was a clinically meaningful difference between the placebo treatment group and the active FemHRT treatment groups in the percentages of patients reporting AEs in the following systems:

- **digestive system [placebo (12%) vs. the 1/5 and 1/10 doses (18 and 29%)]**
  - **nausea and vomiting was noticeably higher (11%) with the 1/10 dose**
- **musculoskeletal system [placebo (5%) vs. all FemHRT groups (13 to 18%)]**
  - **the incidence of myalgia appears to be dose-related**
- **psychobiologic function [placebo (7%) vs. all FemHRT groups (9 to 13%)]**
- **urogenital system [placebo (9%) vs. all FemHRT groups (5 to 27%)]**
  - **the incidence of overall symptoms appears to be dose-related**

6.0 Clinical Study 376-390

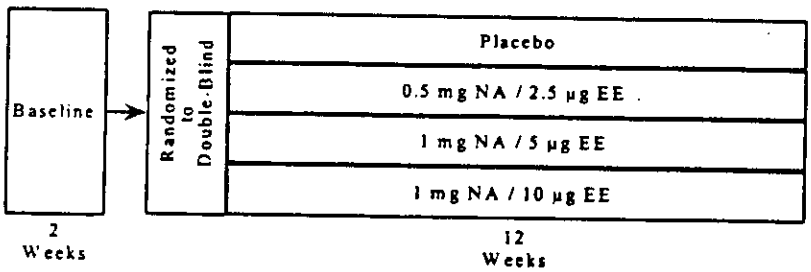
Medical officer comment: the following facts are noteworthy concerning this study:

- **This is the pivotal study for the VMS indication for this NDA; it was carried out between March 1996 and April 1997**
- **The primary efficacy analyses were performed at Week 12; we now recommend that the clinically significant reduction in VMS should occur by Week 4 of therapy and should be maintained throughout 12 weeks of therapy**
- **The sponsor collected and analyzed weekly VMS data from the daily diary cards that were seen at each of the clinic visits (Weeks 2, 4, 8, and 12). Therefore, the sponsor could determine efficacy by Week 4 and ascertain if it was maintained through Week 12.**

6.1 **Objective:** the sponsor's stated objectives were:

- to assess the safety and efficacy of three continuously administered dose combinations of norethindrone acetate/ethinyl estradiol (NA/EE) in reducing the frequency and intensity of hot flashes in postmenopausal women as compared to placebo
- to characterize the population pharmacokinetics (PK) of the same three doses of NA/EE, and investigate a possible relationship between plasma EE concentration and efficacy (hot flash frequency)

6.2 **Study Design:** this was a 12-week, double-blind, randomized, parallel-group, multicenter study at 24 centers in the USA. After completing a 2-week baseline period, eligible subjects were randomly assigned to 1 of 4 treatment groups receiving either placebo or one of the three doses of FemHRT desired for approval (0.5/2.5, 1/5, or 1/10), and entered into a 12-week double-blind period. Subjects recorded daily every evening in their diaries the number and severity of hot flashes and any night sweats or vaginal bleeding/spotting. At subject clinic visits (end of Weeks 2, 4, 8, and 12), all subject diaries were reviewed and the data collected. A blood sample was collected from each woman at baseline and at the end of Weeks 2, 4, and 12 for assay of plasma norethindrone (N) and EE concentrations.



Pharmacokinetics: The population PK of N and EE were characterized using non-linear mixed-effects modeling, including evaluation of relationships between PK parameters and demographic factors, estimation of interindividual and intraindividual variability in PK parameters, and assessment of dose proportionality of plasma N and EE concentrations. In addition, the relationship between hot flash frequencies and plasma EE concentrations was investigated. **See Biopharmacology Review by Venkat Jarugula.**

6.3 **Inclusion Criteria:** women of any race with intact uteri who were at least 40 years of age were included in the study if they:

- Had the onset of menopause (natural or surgical) within 5 years of the study and were amenorrheic
- If amenorrheic for only 6 to 12 months, serum FSH must be ≥50 mIU/ml and estradiol ≤ 25 pg/ml
- Had not used any oral or topical sex hormones for at least 8 weeks before study start, or transdermal hormone therapy for at least 4 weeks
- Had at least 56 moderate to severe hot flashes during the last week of the screening/baseline period

Exclusion Criteria: women were excluded from the study if they had:

- History of breast or ovarian cancer, thromboembolic, cerebrovascular, or coronary artery disease, alcoholism within the previous 3 years, or an autonomic disorder or other disorder associated with VMS not caused by estrogen deficiency
- Current vaginal bleeding, regardless of suspected cause
- Endometrial thickness of >6 mm on transvaginal ultrasound (TVS)
- Mammogram results suspicious of malignant disease
- Uncontrolled hypertension (>150 and/or >90 on two occasions)
- Diabetes mellitus, even if controlled by diet and/or medications
- Liver disease (SGOT and/or SGPT > two times the upper limit of normal and/or bilirubin > 2.4 mg/dL on two consecutive occasions
- Current gallbladder disease, acute or chronic
- Renal disease (BUN >30 mg/dL or serum creatinine > 2.0 mg/dL
- Participated in any other clinical trial within 4 weeks before starting the study

Prohibited medications during the study:

- Any sex hormones (estrogens, progestins, androgens) administered topically, vaginally, or orally
- Hepatic enzyme inducers (e.g., phenobarbital, phenytoin, carbamazepine, rifampin)
- Medications prescribed for the reduction of VMS (e.g., clonidine, lofexidine,veralipride)
- Any other investigational medication

Medical officer comment: the above criteria are acceptable. It is not clear why controlled diabetics were excluded from the study, as this group of women would generally be included in the target population to be treated for postmenopausal vasomotor symptoms and prevention of osteoporosis.

6.4 Study Visits and Procedures: see Table below.

Study Phase	Screening/Baseline		Double-Blind Active Study Period				
Study Day	-28 to -15	-14	1	14	28	56	84
Study Week	-4,-3	-2	0	2	4	8	12
Visit Number	1	2	3	4	5	6	7
Medical History	X						
Physical Exam	X	X					
Pelvic Exam	X	X					
Pap Smear	X	X					
Vaginal Ultrasound	X	X					
Mammography[a]	X.....X						
Hematology	X	X					
Blood Chemistry	X	X					
Urinalysis	X	X					
Serum FSH & E_2	X	X					
Plasma EE /NA (PK)		X		X	X		X
SHBG	X	X					
Medication dispensed			X	X	X	X	
Diary Card Issued	X	X	X	X	X	X	
Clinical Evaluation[b]			X	X	X	X	X
QOL Questionnaire	X		X		X	X	X
AE Reporting	X	X	X	X	X	X	X

[a]Performed between Days –28 and –1. Results of previous mammograms allowed if done within 6 months of study entry.

[b]Includes blood presure, heart rate, and review of diaries.

Primary efficacy parameters as well as hot flash frequency/intensity combination score and QOL data were analyzed using analysis of covariance (ANCOVA). Dunnett's test was used in each analysis to compare each FemHRT dose group with placebo for the primary efficacy parameters and QOL data.

6.5 Population Characteristics and Disposition:

A total of 266 enrolled in the study (average of 66/arm). Baseline characteristics were well balanced between all treatment groups for age, menopausal status (99% natural), and body mass index (median 26 Kg/m^2). The mean age was 51 years, and only one woman was surgically menopausal. Baseline demographics showed the majority of subjects were Caucasian (90%), while 5% were Black, and 5% were Other. The median and mean number of months since all subjects' last menstrual period was 21 and 26 months, respectively. Half (133/266) of the subjects were non-smokers; the other half were roughly evenly distributed between current smokers (27%) and past smokers (23%).

There were 65 to 67 subjects per arm. The percentage of subjects who completed the study was similar across all treatment arms, as well as the percentage of subjects who withdrew prematurely for all reasons. The percentage of subjects who withdrew due to AEs was similar across all treatment groups, and there was no apparent dose-relationship among FemHRT treated subjects in the rate of withdrawal due to AEs. The sponsor table below demonstrates this information.

TABLE: Subject Disposition [Number (%) of Subjects]*

	Placebo	FemHRT (mg NA/mcg EE)			Total
		0.5/2.5	1/5	1/10	
Number Randomized	67	67	67	65	266
Completed Week[a]					
1	67 (100)	67 (100)	64 (96)	63 (97)	261 (98)
4	62 (93)	66 (99)	60 (90)	61 (94)	249 (94)
8	58 (87)	63 (94)	57 (85)	59 (91)	237 (89)
12	45 (67)	55 (82)	45 (67)	53 (82)	198 (74)
Completed Study[b]	57 (85)	60 (90)	55 (82)	58 (89)	230 (87)
Withdrawn Early	10 (15)	7 (10)	12 (18)	7 (11)	36 (14)
Reason for Withdrawal					
Lack of efficacy	2 (3)	1 (2)	3 (5)	0 (0)	6 (2)
Lack of Compliance	1 (2)	1 (2)	0 (0)	2 (3)	4 (2)
Adverse Event	5 (8)	3 (5)	4 (6)	3 (5)	15 (6)
Other/Administrative*	2 (3)	2 (3)	5 (8)	2 (3)	*11 (4)

***This sponsor table is modified by the MO and eliminates data from Weeks 2, 3, 5, 6, 7, 9, 10 and 11.**
[a]Subjects who completed at least the corresponding number of weeks.
[b]Considered completed study if "Completed DB Phase" was checked on case report form.

Medical officer comment: it is important to clarify that while 87% (230/266) of patients completed the study, a smaller percentage (74%, or 198/266) completed Week 12 of drug dosing in the study. It is interesting that it was the middle 1/5 dose of the 3 FemHRT doses that had the poorest completion rate. One would predict this outcome for either the lowest dose (due to less efficacy) or the highest dose (due to more AEs). There is no apparent explanation for this observation.

***Information was requested from the sponsor concerning these 11 withdrawals. Five were lost to follow-up, three withdrew for personal reasons, and three were withdrawn when the sponsor determined that study Site 11 was not compliant to the protocol. Eight different sites had only one**

subject withdraw from the study, so the overall distribution of "administrative" withdrawals was very even, except for study Site 11which had three withdrawals.

Center Enrollment: The 24 centers were spread throughout the USA. The smallest enrollment was 1-2 patients at 4 centers, while the largest 2 enrollments were 30 by Bronsky (Salt Lake City, UT) and 20 by Cohen (Sarasota, FL). The range of percentage completion at a given center was from a low of 64% (9 of 14) to a high of 100% (20 of 20).

Medical officer comment: There did not appear to be any outliers among the 24 centers. The average was 11 women per center; 12 centers enrolled >11, and 12 enrolled ≤ 11 women, so the distribution was even.

6.6 Efficacy Assessments:

The primary efficacy parameters were the weekly hot flash frequency and the average daily intensity of hot flashes over a 7-day period. Weekly hot flash frequency was the sum of each daily frequency as reported in subject diaries over each 7-day period.

The secondary efficacy parameters were the hot flash frequency/intensity combination score (average daily intensity for a given week X average daily frequency), the percentage of subjects with a ≥ 75% reduction (clinical success) or a 100% reduction (elimination) from baseline in weekly hot flash frequency. Additional secondary parameters were the percentage of subjects with night sweats, QOL, and the percentage of subjects with vaginal bleeding/spotting.

Statistical Methods:

The primary analyses and the analyses of clinical success/elimination, hot flash frequency/intensity combination score, and the incidence of night sweats used data from subjects who received at least one dose of study medication (ITT data), with the **primary interest at 12 weeks**. The analyses of quality of life also used ITT data, but the primary interest was at Weeks 4, 8, and 12. Analyses of bleeding/spotting and slopes of quality of life scores used observed-cases data. If no hot flash data were available, or if < 4 days of hot flash data were available for a given week, or if no quality of life data were available at a given visit, data from the most recent week was used, including baseline, if necessary (i.e., LOCF).

6.7 Sponsor Efficacy Results:

Overall, from this study the sponsor claims the following:

- At week 12, FemHRT significantly reduced mean weekly hot flash frequency and mean daily hot flash intensity per week relative to placebo; these reductions were directly dose-related
- At week 12, hot flash clinical success and elimination rates in FemHRT treated subjects were statistically significantly greater than in placebo-treated subjects. FemHRT significantly reduced hot flash frequency /intensity combination scores relative to placebo in a dose-related manner, and fewer FemHRT subjects reported night sweats than did placebo-treated subjects.
- At week 1, 97% of placebo-treated and FemHRT subjects were amenorrheic (no bleeding and/or spotting); by week 12, 95% of placebo and 86% of FemHRT treated subjects (74-93% range) were amenorrheic.
- Statistically significantly greater improvements from baseline in QOL scores as compared with placebo were noted for the vasomotor symptom scale for all FemHRT treatment groups, for the psychosocial and physical scales for the 2.5/0.5 and 10/1 FemHRT groups, and for the sleep scale for the 2.5/0.5 FemHRT dose.

Medical officer comment: it is of note that the FemHRT 1/10 data showed that 56% of the subjects at Week 5 were amenorrheic, and improved to only 74% by Week 12. Both the lower doses showed 80-90% amenorrhea at Week 5 and improved to 90-93% amenorrhea at Week 12. More important to

our division is 12-month cumulative amenorrhea data since this product is intended for longer term use than 12 weeks. Twelve month data is extrapolated from the 2-year –359 clinical trial discussed later in this review.

The primary efficacy parameter data (hot flash frequency and intensity) at 12 weeks is shown in the modified sponsor table below:

HOT FLASH Frequency and Intensity at Baseline and Week 12 (ITT, LOCF)

	Placebo	FemHRT (NA/EE)		
		0.5/2.5	1/5	1/10
Mean Weekly HF Frequency	N= 66	N= 66	N= 65	N= 64
Baseline Mean	85.2	85.8	79.4	91.8
Week 12 Mean	39.4	18.9	13.4	9.8
p-value		0.00*	0.00*	0.00*
Mean Daily HF Intensity per Week				
Baseline Mean	2.4	2.4	2.3	2.4
Week 12 Mean	1.8	1.2	1.0	0.4
p-value		0.01*	0.00*	0.00*

*Statistically significantly less than placebo ($p \leq 0.05$ by Dunnett's test) by ANCOVA
HF = hot flash

Medical officer comment: the efficacy (measured by hot flash frequency and intensity) of FemHRT compared to placebo at Week 12 is clearly demonstrated in the above table. The relationship is dose-related: the higher the dose, the greater the efficacy. In the earlier –368 study the sponsor demonstrated that the 1/0.2 (EE/NA) dose was not effective, so the 2.5/0.5 FemHRT dose is considered by the sponsor to be the lowest effective dose.

The earliest onset of statistically and clinically significant efficacy is also of clinical importance, and this is displayed in the sponsor graph (Figure 6) below showing data for hot flash frequency as determined from weekly diaries.

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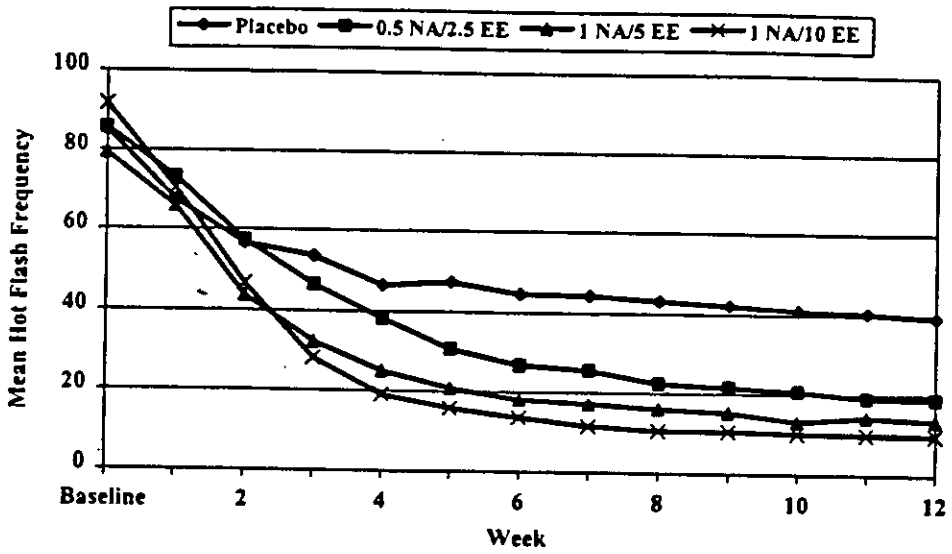


FIGURE 6. **Mean Weekly Hot Flash Frequencies** by Treatment Group (ITT, LOCF)-Study 376-390: 0.5/2.5, 1/5, and 1/10 FemHRT-treated subjects.

Medical officer comment: although Weeks 4 and 8 were not specified by protocol as the primary efficacy time endpoints, it appears that the two higher doses (1/5, 1/10) worked by Week 4 and efficacy was maintained through Week 12. There was no clinical difference between the 1/5 and 1/10 doses. The lowest dose of FemHRT (0.5/2.5) appeared to work slightly slower, by Week 5-6, and was maintained through Week 12.

FemHRT-related reductions from baseline in mean daily hot flash intensity per week is shown in the sponsor's graph below (Figure 8).

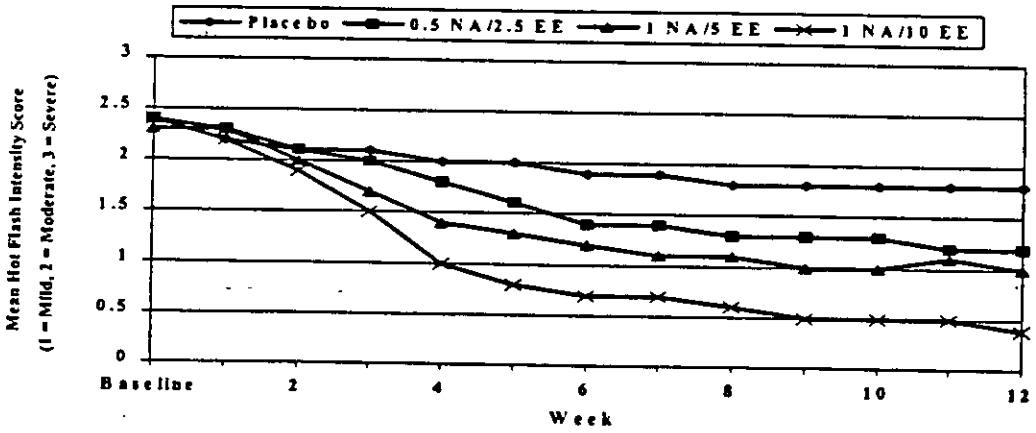


FIGURE 8. **Mean Weekly Hot Flash Intensities** by Treatment Group (ITT, LOCF): Study 376-390

Medical officer comment: combining the data from the above two graphs for weekly changes in the frequency and intensity of hot flashes for the three FemHRT doses compared to placebo, we conclude the following that should be reflected in the label. For treating vasomotor symptoms associated with the menopause:

- [redacted]
- **The FemHRT 1/5 and [redacted] doses differed significantly from placebo by week 3-4 of treatment and were maintained through Week 12**
- **In general, the [redacted] 1/5 and [redacted] showed the same clinical results in the treatment of vasomotor symptoms**
- [redacted]

[redacted]

6.7 Sponsor Safety Analysis:

Overall, from this study the sponsor summarized the following safety conclusions:

- Most AEs were mild to moderate in severity
- Serious AE rates were evenly distributed across all treatment groups, as were rates of withdrawal due to all AEs and drug-related AEs. There were no drug-related serious AEs, and there were no deaths.
- The most frequent drug-related AEs reported by FemHRT treated subjects were headaches (7%) and breast pain (5%); of these, only breast pain appeared to be dose-related.
- Three AEs were judged by the Medical Monitor as possibly clinically important. These 3 events resolved and were considered possibly drug-related:
  - Severe superficial thrombophlebitis and an ovarian cyst in a 1/5 treated subject
  - Mild heart palpitations in a 1/5 treated subject
  - Severe, rapid heart beat in a 1/10 treated subject
- Possibly clinically important changes in lab values included dose-related increases in the frequency of FemHRT treated subjects with increased blood glucose levels and decreased hematocrit.
- Mean follow-up coagulation factors and liver function values in all treatment groups were, overall, less than or nearly identical to mean baseline values. There were no clinically significant changes from baseline in any coagulation factor in FemHRT treated subjects, although one subject, mentioned above, experienced a severe superficial thrombophlebitis.

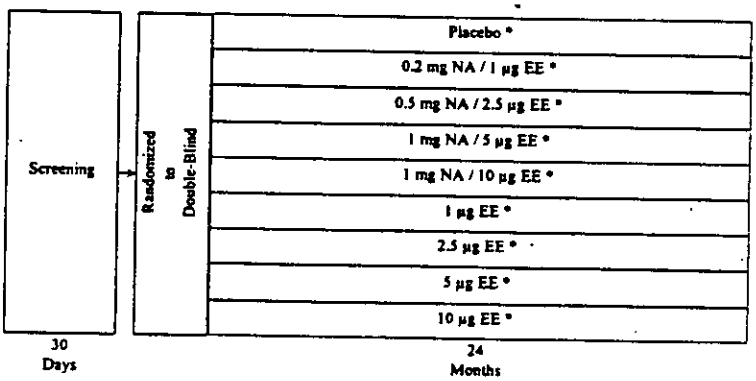
Medical officer comment: the above conclusions have been reviewed and are acceptable. A medical officer overview of the safety data from all the clinical studies in this NDA is found in section 9.0 at the end of this review.

7.0 Clinical Study 376-359

7.1 Objectives: the sponsor's stated objectives were:

- to compare the efficacy in maintaining BMD of 4 dosage combinations of EE and NA with that of placebo;
- to demonstrate the protective effect on the endometrium of continuous administration of 4 dosage combinations of FemHRT compared with 4 corresponding doses of unopposed EE;
- to assess the safety of EE /NA;
- to evaluate changes in selected lipid parameters.

7.2 Study Design: this was a 2-year, randomized, placebo-controlled, double-blind, parallel-group, multicenter study carried out at 80 centers between July 1989 and August 1993. Subjects were randomly assigned to 1 of 9 groups receiving either placebo, FemHRT (0.2/1, 0.5/2.5, 1/5, or 1/10), or unopposed estrogen (1, 2.5, 5, or 10 µg). All subjects received calcium, 1000 mg daily in divided doses. After completing a 30-day screening period, qualifying subjects entered a 24-month double-blind period. Subjects assigned to the 10 µg EE dosage group were discontinued midway through the study (at 12 months) due to a rate of endometrial hyperplasia that exceeded the protocol-specified level.



Medical officer comment: the following facts are noteworthy concerning this study:

- **Endometrial biopsies were done every six months, i.e., at 6, 12, 18 and 24 months allowing for as many as four biopsies per subject and a 2-year follow-up for endometrial hyperplasia**
- **4 unopposed estrogen arms allowed for good comparative data for each potential FemHRT arm**
- **BMD data was obtained at 12 and 24 months**
- **Large study (1265 subjects), placebo-controlled**

7.3 Inclusion Criteria: asymptomatic or mildly symptomatic postmenopausal women with an intact uterus; same as the criteria listed on pages 15-16 for study 376-390, with the following exceptions:

- must have stopped taking sex hormones (estrogens or progestins) or calcitonin 6 months before starting the study
- must have FSH ≥ 40 mIU/mL, serum estradiol ≤ 20 pg/mL (amended to ≤ 40), lumbar spine trabecular bone densities between 90-160 mg/cm^3 by quantitative cat (QCT) scan, and atrophic endometrial biopsies
- must be within 20% of ideal body weight

Exclusion Criteria: subjects with a history of or current breast cancer; diabetes mellitus; uncontrolled hypertension; alcoholism; or thromboembolic, cerebrovascular, liver, gall bladder, or coronary artery disease. Other exclusion criteria included:

- current vaginal bleeding
- suspicious mammogram findings
- significant VMS requiring medical treatment
- diseases that could affect bone metabolism
- chronic use of medications that could affect bone-calcium metabolism

Prohibited medications during the study:

- any sex hormones administered topically, vaginally, or orally other than study medications
- medications that could affect bone-calcium metabolism
- medications that might lower serum lipids

7.4 Population Characteristics and Disposition: a total of 1265 women started this 9-arm study with 824 (65%) completing the two-year mark. The enrollment ranged from 136 to 146 subjects per arm. The reason for this difference of 10 subjects is because 80 centers were involved in the study and randomization resulted in a slightly uneven distribution. No one in the unopposed 10 mcg EE arm completed the study because midway through the study the sponsor discontinued this group due to unacceptably high rates of endometrial hyperplasia. The majority of the women enrolled in the study were white (95%) with a mean age of 52 years. The mean length of time since the LMP was 31 months. Smoking history showed that 45% had never smoked, 31% were past smokers, and 24% were current smokers. Patients had discontinued use of sex hormones at least 6 months before randomization into the study. About a third of the women in each treatment group had previously received hormone replacement therapy, most commonly conjugated estrogens and medroxyprogesterone acetate.

Baseline mean BMD was comparable for all treatment groups. Ninety-six (67%) patients were active in the 10 mcg EE treatment group when that group was terminated by the sponsor due to an unacceptably high rate of endometrial hyperplasia as specified by the protocol. There were no clinically meaningful differences between the 554 women with evaluable endometrial biopsy data and all patients randomized to treatment. Withdrawal rates ranged from 22% to 30% in the eight active treatment groups. Conversely, completion rates at 24 months ranged from 70-78%.

Medical officer comment: given the facts that this was a 24 month study in postmenopausal women, requiring a daily medication, three measurements for BMD, and five endometrial biopsies, the overall completion rates in each treatment group were acceptable. The patient population was 95% Caucasian which is not representative of the target population of postmenopausal women. The percentage of Caucasian women in other recent studies submitted to the FDA for estrogen replacement therapy and hormone replacement therapy, however, has ranged from 90 to 95%.

7.5 Study Procedures (Parameters) and Study Visits: for all parameters except for vaginal bleeding/spotting, if the patient had multiple visits within a time window, then data from the last visit were used for analysis and summarization. For vaginal bleeding/spotting, all data in a time window were used for summarization. For the endometrial data, patients that were censored due to bleeding or hyperplasia had their last observation carried forward into all time intervals for all analyses. Also, for the endometrial data, if the biopsy was classified as insufficient for definitive diagnosis, it was treated as missing data and excluded from all analyses. The timing per protocol of the 4 major parameters is listed below:

- Endometrial effects: baseline and months 6, 12, 18, and 24
- Bone-mineral density measurement: baseline and months 12 and 24
- Lipid values: baseline and months 12 and 24
- Vaginal bleeding and/or spotting: months 1, 3, 6, 12, 18, and 24

7.6 Efficacy Assessments and Statistical Methods: discussion here centers on the analysis of endometrial effects. All comments concerning BMD and osteoporosis prevention are found in the medical officer review from the Endocrine and Metabolic Division (DMEDP). To be included in the observed case analysis for endometrial effects, patients must have taken at least 1 dose of study medication, had an atrophic baseline biopsy, and had a follow-up biopsy within a specified time window. For the ITT analysis of endometrial effects, patients were required to have taken at least one dose of study medication, had an atrophic biopsy, and at least one follow-up biopsy (LOCF).

Medical officer comment: a baseline biopsy is expected to be atrophic (normal) because all of the subjects were postmenopausal. Insufficient tissue and proliferative tissue are also considered normal in postmenopausal women on hormone replacement therapy. However, insufficient tissue raises the

possibility that the biopsy was inadequate or invalid because it was not properly performed. Proliferative tissue means that there is enough endometrial growth that some degree of hormonal (estrogenic) effect is present. Any degree of endometrial hyperplasia and/or atypia is definitely abnormal.

An interim analysis of endometrial effects at Month 12 was planned in the protocol. However, this analysis was not conducted because too few endometrial endpoints had occurred to make the interim analysis results potentially useful. Since the 10 mcg EE treatment group was terminated due to an unacceptable endometrial hyperplasia rate as specified in the protocol, thereby partially unblinding the study, all statistical testing of endometrial effects was done using a significance level of 0.045. All other statistical testing was done using a significance level of 0.05.

The diagnosis of hyperplasia as determined by endometrial biopsy was the primary endpoint. Endometrial biopsies were done at screening and every 6 months. Month 24 was the primary time point. The percentage of patients with hyperplasia was analyzed using categorical data methods. The primary comparisons of interest were each NA/EE treatment group versus the corresponding unopposed EE group, dose response within the NA/EE treatment groups, and comparisons to the placebo group. Each NA/EE treatment group versus the corresponding EE treatment group was tested using Fisher's Exact Test for 2 by 2 tables. No p-value adjustments due to the multiple comparisons were made.

As a supplemental analysis, planned prior to completion of the study, endometrial response was modeled using analysis of variance including the effects of treatment and center. For the analysis, endometrial proliferation categories were assigned scores of 1 = atrophic, 2 = mildly proliferative, 3 = moderately proliferative, 4 = markedly proliferative, and 5 = hyperplastic. The categories of early secretory, intermediate secretory, and late secretory were collapsed into the atrophic category. Analyses were performed on the evaluable data at the Months 12 and 24 time points only. Comparisons of interest were the same as the comparisons for hyperplasia.

Patients were questioned retrospectively for the occurrence of vaginal bleeding/spotting and the number of days per month of bleeding/spotting at every scheduled clinic visit (Month 1, 3, 6, 12, 18, and 24). The evaluation of bleeding/spotting was done descriptively without the use of statistical testing. The number and percent of patients reporting bleeding/spotting at least once within a time window was summarized by treatment group. For the patients that reported bleeding/spotting within a time window, the average monthly duration of the bleeding/spotting was computed in days. If a patient had multiple clinic visits within a time window, the average duration was computed for the patient before computing an average for each treatment group.

7.7 Sponsor Efficacy Results

Primary Measure of Efficacy: Endometrial Hyperplasia

All patients with hyperplasia on any endometrial biopsy were included in analyses of evaluable data and were carried forward for all time points. A statistically significantly greater percentage of patients developed hyperplasia in the 10 mcg EE treatment group compared to the 1/10 FemHRT treatment group at all time points. The 10 mcg EE group was terminated for safety reasons after 12 months due to an unacceptably high rate of hyperplasia specified by protocol (>6%). Overall, 14 patients developed hyperplasia in the EE treatment groups compared to only one patient in the NA/EE (FemHRT) groups. Of the 14 cases of hyperplasia in the unopposed EE groups, 10 were diagnosed by Month 12. The only patient with definite hyperplasia in the NA/EE group was taking the 0.2/1 dose; this patient had also been using a vaginal estrogen cream for approximately 8 weeks prior to the abnormal biopsy. In addition, 1 patient developed hyperplasia in the placebo group.

The following table, modified by the medical officer, is a summary of the endometrial biopsy evaluable data broken down simply as insufficient tissue, atrophic tissue, and endometrial hyperplasia:

Endometrial Biopsies and Women with Endometrial Proliferation/Hyperplasia[a]

Time (month)	Placebo	FemHRT (NA mg/ EE mcg)			EE mcg		
		0.5/2.5	1/5	1/10	2.5	5	10[b]
Month 0							
N= number randomized	137	136	146	145	137	141	143
Biopsy attempts	134	133	143	142	134	139	140
Insufficient tissue	4	18	7	11	3	8	9
Atrophic tissue	130	115	136	131	131	131	131
Endometrial hyperplasia	0	0	0	0	0	0	0
Month 12							
N= Patients biopsied (% of # randomized)	113 (82)	104 (76)	110 (75)	109 (75)	110 (80)	114 (81)	65 (44)
Evaluable biopsies	83	69	65	71	90	94	61*
Proliferative tissue	23	28	24	34	75	91	51
Atrophic tissue	60	41	41	37	15	2	1
Endometrial hyperplasia	0	0	0	0	0	1	9*
Insufficient tissue	30	35	45	38	20	20	4
Month 24							
N= Patients biopsied (% of # randomized)	94 (69)	99 (73)	102 (70)	99 (68)	90 (66)	107 (76)	19 (13)
Evaluable biopsies	59	57	65	65	67	90	18*
Proliferative tissue	20	27	32	28	60	86	8
Atrophic tissue	38	30	33	37	6	2	0
Endometrial hyperplasia	1	0	0	0	1*	2*	10*
Insufficient tissue	35	42	37	34	23	18	2
No tissue OR No biopsy done	39	35	42	39	46	33	118*
Completed Study N=number (%)	108 (79)	103 (76)	105 (72)	103 (71)	96 (70)	104 (74)	4* (3)

[a]All patients with hyperplasia were carried forward for all time points.
[b]The 10 mcg EE group was terminated early for safety reasons due to the high rate of hyperplasia.
*p-value ≤ 0.045 for 1-sided test that percent of patients with hyperplasia in EE treatment group was > the percentage in the corresponding EE /NA treatment group per protocol.

MEDICAL OFFICER Comments: the following interpretations are of note concerning the above:

- **All subjects had a baseline atrophic (normal) endometrial biopsy**
-
- **There were no cases of endometrial hyperplasia in the 3 FemHRT doses during the 24 months studied with endometrial biopsies from as many as 4 time points in 311 women**
- **The highest dose of unopposed EE (10 mcg) corresponded to an increasing percentage of patients with hyperplasia; however, the mid and lower doses (5 and 2.5 mcg) did not**
- **The one placebo patient with hyperplasia had no known risk factors**

- **The data on endometrial biopsies at Months 6 and 18 are not shown in the above table, but the data was included in the original sponsor's table**

Secondary Measures of Efficacy: Endometrial Proliferation Status

Endometrial status was evaluated using the following categories: atrophic [normal in postmenopausal women]; mildly, moderately, and markedly proliferative [showing hormonal effect and endometrial growth]; and hyperplastic [abnormal, showing high estrogenic effect]. At months 12 and 24, the percentage of patients with atrophic biopsies was approximately the same across the FemHRT treatment groups (range was 51 to 63%) with the lowest percentage (51%) observed in the 1/5 group at Month 24. In contrast, by Month 12, the percentage of patients with an atrophic biopsy in the unopposed EE groups was 43% in the 1 mcg EE group and decreased in a dose-related fashion down to only 2% in the 10 mcg EE group. Given the fact that patients were required to have an atrophic endometrial at the time of enrollment, a shift in the distribution of endometrial status is indicative of an estrogenic effect. This effect can be seen in the shift from atrophic to greater than mildly proliferative or hyperplastic in the unopposed EE treatment group (range from 23 to 80% at Month 12; from 26 to 100% at Month 24). By comparison, the FemHRT groups had fewer patients with at least moderate proliferative endometrial changes (range from 4-6% at Month 12 and 4-5% at Month 24). The shift to at least moderately proliferative endometrial findings in the unopposed EE groups was directly dose-related. These results were confirmed in the analyses of the observed cases and ITT population.

In order to summarize shifts in the distribution of endometrial status, scores were assigned by the sponsor, ranging from 1 = atrophic; 2, 3, 4 = mild, moderate, and marked proliferation, to 5 = hyperplastic. The analysis of biopsy severity scores substantiated the protective effect on the endometrium provided by NA compared to unopposed EE treatment. At Months 12 and 24, all EE treatment groups had statistically significantly greater mean biopsy severity scores compared to the corresponding FemHRT groups. At Month 12, adjusted mean biopsy scores for all three FemHRT groups were approximately the same (~1.45) with the highest score 1.52 for the 1/10 dose, and the lowest score 1.41 for the 1/5 dose. Higher scores correlate with endometrial growth that is less desirable because of the risk of hyperplasia and endometrial cancer. In contrast, at Month 12, mean biopsy scores increased in a linear manner from 1.64 in the 1 mcg EE group to 3.21(at least moderate proliferative changes) in the 10 mcg EE group.

The table below, modified by the medical officer, shows a breakdown of the evaluable endometrial biopsy results at Months 12 and 24. Data was also available at Month 6 and 18, but is not included in the table.

Summary of Evaluable Endometrial Biopsy Results at Month 12 and 24
[Number (%) of Patients]

Time (month)	Placebo	FemHRT (NA mg/ EE mcg)			EE mcg		
		0.5/2.5	1/5	1/10	2.5	5	10[a]
Month 0							
N= number randomized	**137**	**136**	**146**	**145**	**137**	**141**	**147**
N= biopsy attempts	**134**	**133**	**143**	**142**	**134**	**139**	**140**
Insufficient tissue	4	18	7	11	3	8	9
Atrophic tissue	130	115	136	131	131	131	131
Endometrial hyperplasia	0	0	0	0	0	0	0
Month 12							
N[b]= evaluable biopsies	**83**	**69**	**65**	**71**	**90**	**94**	**61***
Atrophic tissue	60 (72)	41 (59)	41 (63)	37 (52)	15	2	1
Proliferative							
Mild	18	25 (36)	21 (32)	30 (42)	54	40	10
Moderate	5	3 (4)	3 (5)	4 (6)	19	47	33
Marked	0	0	0	0	2	4	7
Secretory	0	0	0	0	0	0	1
Hyperplastic[c]	0	0	0	0	0	1	9*
N= Insufficient tissue	30	35	45	38	20	21	6
Month 24							
N[b]= evaluable biopsies	**59**	**57**	**65**	**65**	**67**	**90**	**18***
Atrophic tissue	38 (64)	30 (53)	33 (51)	37 (60)	6	2	0
Proliferative							
Mild	18 (31)	25 (44)	29 (45)	25 (38)	43	36	0
Moderate	2 (3)	2 (4)	3 (5)	3 (5)	17	46	6
Marked	0	0	0	0	0	4	1
Secretory	0	0	0	0	0	0	1
Hyperplastic[c]	1 (2)	0	0	0	1*	2*	10*
N= Insufficient tissue	35	42	37	34	23	18	2
Completed Study N=number (%)	108 (79)	103 (76)	105 (72)	103 (71)	96 (70)	104 (74)	4* (3)

*The 10 mcg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia
[b]Excludes patients with missing or insufficient biopsies
[c]Cases of endometrial hyperplasia were carried forward for each time point analysis

Medical officer comment: the above data and scoring system helps confirm the endometrial protection provided by all three doses of FemHRT over the 12-24 month period of time. It also demonstrates the proliferative and hyperplastic dose-related effect of unopposed ethinyl estradiol on the endometrium in postmenopausal women.

Another concern with the above data is the missing data; namely, how do we interpret those patients who did not have a biopsy or whose biopsy showed no tissue? Since interpretation of missing data is purely speculative, we simply counted it as no data and made no assumptions concerning the results. It is important to note that all patients here with endometrial hyperplasia were carried forward for all time points. So, even if the hyperplasia might have spontaneously reverted to the baseline atrophic (normal) tissue, this possibility was not allowed per protocol and per study analysis.

Secondary Measures of Efficacy: Patients Withdrawal due to Bleeding

The numbers of patients withdrawing from the study due to bleeding were similar for NA/EE and corresponding EE treatment groups. The 0.5/2.5 dose had one patient withdrawal, while there were none in the 2.5 EE group; **the 1/5 and 5mcg EE groups each had 2 patient withdrawals, and the 1/10 and 10 mcg EE groups each had 8 patient withdrawals.** All of the 8 patients from the 1/10 FemHRT group withdrew by the end of Month 4 (Day 128), and 6 of these patients withdrew before Day 76. In contrast, the earliest patient withdrawal from the 10 mcg EE group occurred on Day 95, and 5 of the 8 patients withdrawing due to bleeding withdrew after Day 250 (Month 8).

Secondary Measures of Efficacy: Vaginal Bleeding and/or Spotting

More patients in the FemHRT treatment groups reported vaginal bleeding/spotting in the earlier months of the study than patients in the EE groups. The number of patients in the FemHRT groups reporting bleeding/spotting decreased during the study such that at Month 24, fewer than 13% of patients in any group reported bleeding/spotting, with 0.6 to 2.1 average number of days per month. By Month 24, the percentage of 0.5/2.5 and 1/5 FemHRT subjects who were amenorrheic was similar to the percentage of corresponding EE subjects. Larger percentages of patients ≤ 1 year since menopause at screening reported bleeding/spotting compared with patients > 1 year since menopause.

Summary of Vaginal Bleeding/Spotting (B/S) with ITT Population over 24 Months*

Time	Placebo	FemHRT (NA mg/EE mcg)*			Ethinyl estradiol (EE), mcg		
		0.5/2.5	1/5	1/10	2.5	5	10
Month 1							
N	136	134	143	140	133	139	139
N (%) with B/S	8 (6)	18 (13)	58 (41)	55 (39)	9 (7)	12 (9)	13 (9)
Month 3							
N	124	127	129	126	124	132	125
N (%) with B/S	5 (4)	22 (17)	49 (38)	59 (47)	8 (6)	12 (9)	29 (23)
Month 6							
N	127	123	127	123	125	129	126
N (%) with B/S	8 (6)	16 (13)	31 (24)	39 (32)	8 (6)	16 (12)	44 (35)
Month 12							
N (% of Mo. 1)	123 (90)	116 (87)	125 (87)	113 (81)	116 (87)	125 (90)	78 (56)
N (%) with B/S	16 (13)	22 (19)	30 (24)	38 (34)	10 (9)	19 (15)	25 (32)
Month 18							
N	109 (80)	103 (77)	111 (78)	113 (81)	105 (79)	110 (79)	32 (23)
N (%) with B/S	5 (5)	7 (7)	18 (16)	27 (27)	7 (7)	11 (10)	10 (31)
Month 24							

N	110	104	107	104	97	106	11
N (%) with B/S	5 (5)	10 (10)	13 (12)	11 (11)	6 (6)	13 (12)	5 (45)

*The 10 mcg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia. Data from the 1 mcg EE group is not included in this table.
*This table is modified by the MO. Data from the 0.2 mg NA/1 mcg EE group and from the number of days of B/S per month are not included in this table.

Medical officer comment: the sponsor presented the above table showing the subjects who experienced bleeding/spotting. Clinic visits were at the end of Months 1, 3, 6, 9, 12, 18, and 24 of the study. At each visit "absence or presence (number of days per month) of vaginal bleeding and/or spotting were recorded." It is unclear from the protocol if the data collection for bleeding/spotting was from patient recall or daily diary cards. The sponsor has confirmed by teleconference that this data was by recall, which represents a flaw in the design of the study.

It is noteworthy that at both Months 12 and 24 there was a range of only 6 to 15% of the women taking unopposed EE, 2.5 or 5.0 mcg, who experienced vaginal bleeding/spotting. A higher percentage would normally be expected. By contrast, 24% of FemHRT 1/5 subjects experienced bleeding/spotting at Month 6 and 12, and 12% at Month 24. This is much higher than the corresponding unopposed EE group. Even worse, 32 and 34% of FemHRT 1/10 subjects experienced bleeding/spotting at Months 6 and 12, and 11% at Month 24. Thus the FemHRT 1/10 had a worse bleeding profile compared to FemHRT 1/5 from Months 3 through at least Month 18 (data shown in the above table). Further evidence of the problem of bleeding while on 1/10 is the 8 patients who withdrew from the study due to bleeding compared to only 2 withdrawals on the 1/5 dose.

Throughout the ISE, the sponsor consistently compares each NA/EE dose with the corresponding unopposed EE dose, but not with each other. Since the FDA objective is to approve the lowest and safest effective dose of a medication for any specific indication, our comparisons are often between similar doses, such as FemHRT 1/5

Additional Efficacy Parameter: Lipids

The sample size was not derived to look at serum lipid endpoints or to determine equivalence between groups. Therefore, inferential statistics were done, but not used to interpret the results. With the large sample size, very small, clinically insignificant changes in lipid values would be expected to show statistical significance, so the following sponsor table provides descriptive summary information with regard to these parameters. Mean baseline lipid parameter values were similar across treatment groups and in the ranges expected for this population. Mean plasma total cholesterol values ranged from 212 to 222 mg/dL, which is considered to be in the normal range for women aged 50 to 54. Mean plasma triglyceride values ranged from 99 to 114 mg/dL, which is lower than the expected mean triglyceride of 115 mg/dL for women in this age range.

At Months 12 and 24, reductions from baseline in LDL-C were observed for all active treatment groups. At Month 24, in the placebo group there was a small increase in LDL-C (0.6 mg/dL, 1%). Mean changes and mean percent changes from baseline were similar for FemHRT and corresponding EE treatment groups. The largest decreases in LDL-C occurred with intermediate doses of both NA/EE and EE with reductions from baseline of 12.3 mg/dL (7.5%) in the FemHRT 1/5 dose and 11.4 mg/dL (6.8%) in the corresponding 5 mcg EE group.

Increases from baseline in HDL-C appeared dose-related with EE treatment up to 5 mcg EE at both Months 12 and 24. For the placebo group, there was a decrease of 4% in HDL-C at Month 12 followed by basically no change from baseline (+0.1%) at Month 24.

TABLE 4. Mean % Change From Baseline Lipid Profile. Values After 12 and 24 Months of Treatment With FemHRT*

Lipid Parameter	Placebo	FemHRT (mg NA/μg EE)		
		0.5/2.5	1/5	1/10
@ Month 12	N = 124	N = 123	N = 128	N = 125
Total Cholesterol (mg/dL)	-1.4%	-8.4	-9.7	-4.6
HDL-C (mg/dL)	-3.8	-6.6	-11.8	-5.9
LDL-C (mg/dL)	-1.5	-9.8	-9.5	-4.9
Triglycerides (mg/dL)	+15.4	+8.3	+10.5	+24.1
HDL/LDL ratio	0	+5.0	+1.0	+2.0
@ Month 24	N = 129	N = 128	N = 132	N = 129
Total Cholesterol* (mg/dL)	+2.5%	-12.5%	-16.6%	-3.7%
HDL-C* (mg/dL)	0.1	-1.1	-4.8	-0.7
LDL-C (mg/dL)	0.6	-12.1	-12.3	-6.3
Triglycerides* (mg/dL)	14.1	2.7	3.0	20.8
HDL/LDL ratio	+2.0	+11	+4.0	+8.0

NA = Norethindrone acetate.
EE = Ethinyl estradiol.
*ITT population, study 376-359; data from the ISE and Vol. 77

Medical officer comment: while the above table, modified by the MO, does not show the changes in the corresponding unopposed EE treatment groups, the data from the 2-year clinical trial as presented by the sponsor in their discussions and in the above table was not very convincing:

- **there is no clear dose-responsiveness for any of the above parameters; it is hard to differentiate possible drug effect from random data**
- **the label should reflect that these women had normal cholesterol profiles at baseline**
- **the clinical relevance of such modest decreases in LDL-C, especially in light of the decreases in HDL-L, is unknown**
- **the overall effect of FemHRT does not appear to be harmful, except to note the 21% mean change from baseline in triglycerides with the FemHRT 1/10 dose**

Other Secondary Parameters:

The study also evaluated vaginal dryness, "global assessment," and Quality of Life. In summary, the sponsor claims that the findings demonstrate the following:

- The percentage of FemHRT-treated subjects reporting vaginal dryness during the study appeared to be somewhat less than placebo-treated subjects, although the study was not designed with this endpoint in mind
- The percentage of FemHRT-treated subjects reporting improvement in menopausal symptoms was significantly greater than placebo-treated subjects
- FemHRT-treated subjects demonstrated statistically significantly greater improvements from baseline in the vasomotor QOL scale as compared with placebo-treated subjects; 0.5/2.5 and 1/10 FemHRT-treated subjects demonstrated statistically significantly greater improvements in the psychosocial and physical scales; and 0.5/2.5 FemHRT-treated subjects demonstrated statistically significantly greater improvements in the sleep scale.

Medical officer comment: all of the above improvements are expected with estrogen replacement therapy and hormone replacement therapy. It is unclear why the two higher FemHRT doses did not significantly improve the sleep scale, but the effect still showed some improvement.

7.8 Sponsor's Safety Results

Overview: Although 84% of patients reported AEs, less than half of the patients experienced AEs considered associated with study medication. The placebo group had the smallest percentage of patients with associated AEs and, for the other treatment groups, AE event rates appear to be dose-related. Many of the AEs were common to hormone replacement therapy. The majority of AEs were mild or moderate in intensity for all treatment groups and the percentage of patients with severe AEs was similar among all groups. Excluding those events that were "definitely not related to study medication," 2% of patients had serious AEs. Events reported by the largest percentage of patients and considered severe and associated with study drug were (in descending order): headache, breast pain, abdominal pain, and depression. There were three deaths (one stomach cancer, one lung cancer, one C5-6 fracture) during the study, none related to treatment.

Patients Withdrawals: **Fourteen percent of patients withdrew from the study due to AEs.** Although withdrawals were relatively evenly distributed among treatment groups, a larger percentage of patients in the higher dose groups withdrew due to AEs. Because there were a relatively small number of nonwhite patients and a limited age range in the study population, no analyses of AEs by race or age were carried out in the NDA.

Most Common AEs: **Headache was the most common AE reported overall** (268/1265 = 21%), and in each treatment group except for patients in the placebo (19%) and 10 mcg EE (17%) groups. The most common AE in the placebo group was rhinitis (30/137 = 22%), and the 10 mcg EE group was myalgia (27/143 = 19%). Other AEs reported by > 8% of patients included in descending order of overall frequency: rhinitis (18%), sinusitis (14%), myalgia (13%), breast pain (12%), viral infection (11%), abdominal pain (11%), and nausea and/or vomiting (9%). Hot flashes were also reported, but it was not possible to differentiate this finding as an AE or a symptom of the condition being treated.

Associated AEs included those considered by the investigator as possibly, probably, or definitely related to study drug. Overall, **breast pain was the most common associated event (131/1265 = 10%).** It was reported by a higher percentage of FemHRT patients compared to placebo or EE patients and appeared to be dose-related. Because breast tenderness is a common AE associated with estrogen replacement therapy, however, this AE is not unexpected. Other associated AEs most commonly reported were generalized edema, abdominal pain, nausea and vomiting, weight gain, and headache. Since these reactions are also associated with hormone therapy, they were not unexpected in this study population.

Breast Cancer: Six patients associated with 6 different treatment groups (3 EE and 3 NA/EE) were diagnosed as having breast cancer. The range of treatment time for these patients was 5+ months to 24 months. For 5 of the 6 women, the relationship to study drug was considered unlikely, not related, or unknown.

Medical officer comment: There were actually 4 patients (not 3) on FemHRT in this study with breast cancer. The sponsor calculated that the smaller number of breast cancer cases was not statistically significantly different from what would be expected based on NCI-SEER data (based on a sample of 10% of the US population). Confidence intervals around the sponsor's calculation, however, were not provided. The number of breast cancer cases associated with this product and other HRT products will need to be monitored carefully in the future. It is hard for this reviewer to agree with the sponsor's assessment that there is no relationship between breast cancer and FemHRT.

Endometrial Hyperplasia: 14 of the 16 cases of endometrial hyperplasia were found in the unopposed estrogen treatment groups. Of these 14, 10 were in the EE 10 mcg group. After confirmation of hyperplasia, most patients were placed on progestin therapy; all had follow-up biopsies. For 13 of 16 patients, no further treatment was given after the progestin therapy. Two patients received further hormone therapy and 1 had a hysterectomy for uncontrolled bleeding. In addition to the 16 hyperplasia cases, 1 patient in the lowest NA/EE group (0.2/1) had an endometrial polyp with focal hyperplasia, and 1 patient* in the FemHRT 1/5

group developed what was thought to be mild focal hyperplasia with mildly proliferative endometrium determined by biopsy. See comments that follow.

Medical officer comment: as already discussed in the efficacy section for this study, it is clearly demonstrated that FemHRT provides adequate endometrial protection at all three doses for up to 24 months. Therefore, the safety issue of undesired or unacceptable endometrial changes due to hormone replacement therapy has been answered. It is of note, however, that there was only 1 case of endometrial hyperplasia in the combined 184 unopposed EE 2.5 and 5 mcg subjects at Month 12, and 3 cases in 157 (3%) unopposed EE 2.5 and 5 mcg subjects at Month 24. This raises the question of the need for any progestin for endometrial protection at these two lower ethinyl estradiol doses.

***This patient was a 53 year old Caucasian woman on FemHRT 1/5. Her endometrial biopsy on Day 343 showed some abnormal glandular tissue with either hyperplasia or a neoplasm of endometrial or endocervical origin. A colposcopy and fractional D&C were performed on Day 357. This revealed benign results (squamous metaplasia and proliferative endometrium). The investigator considered the focal hyperplasia to be endocervical and mild in intensity and probably related to the study drug.**

Mammogram abnormalities: mammograms were performed on each patient within 0-6 months before study entry. Mammography was repeated at the end of Months 12 and 24 or at the time of termination if the patients withdrew from the study. The overall number of abnormalities were categorized into 5 major categories: fibrocystic changes (363/1265 = 29%), fibroadenosis (33 = 3%), calcifications (228 = 18%), ductal hyperplasia (2 = 0%), and density (118 = 15%). All treatment groups and the placebo group were comparable with regard to the type and number of abnormalities observed prior to treatment. As noted, the greatest number of abnormalities were for fibrocystic changes, calcifications, and density. The pattern of abnormalities was maintained during the study and there was no shift in preponderance of abnormality by treatment. Thus, there did not appear to be any dose-related effect on mammography abnormalities in either the FemHRT or the unopposed EE groups.

Thromboembolic events: during the study two patients reported AEs related to potential formation of a thrombus. One FemHRT 1/5 patient (current smoker) developed the serious AE of a DVT; one patient on FemHRT 1/10 (past smoker) had a superficial phlebitis and withdrew from the study. The investigator considered the events were possibly or probably related to study medication.

Four patients, 2 in the FemHRT and 2 in the EE treatment groups, had embolic AEs. Both FemHRT patients had a history of smoking; one woman on 0.2/1 developed a serious AE of left-sided weakness (possible stroke), and the other on 0.5/2.5 had a transient ischemic attack. Both patients recovered from the events. Both ethinyl estradiol patients had a history of smoking; one woman on 2.5 mcg EE developed a sudden onset of right arm and leg weakness, and the other on 5 mcg EE developed a severe TIA on Day 57 of treatment. Both patients recovered from the events. All 4 "embolic events" were considered possibly related to study medication.

Medical officer comment: the overall safety profile for FemHRT in this study is acceptable. FemHRT was comparable to placebo and unopposed ethinyl estradiol for the most common AEs (headache, rhinitis, sinusitis, myalgia, breast pain, viral infection, abdominal pain, N&V). The majority of AEs were mild to moderate for all treatment groups and the percentage of patients with severe AEs was similar among groups. The percentage of patients with serious AEs and the type of serious AEs were evenly distributed. Further discussion of the overall safety profile and thromboembolic events for FemHRT is found at the end of this review.

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8.0 MEDICAL OFFICER OVERVIEW OF EFFICACY

Parke-Davis' FemHRT™ is a continuous orally-administered, once daily, combination hormone replacement therapy tablet, composed of norethindrone acetate (mg NA) and ethinyl estradiol (µg EE). FemHRT was investigated in 4 clinical studies (376-343, -359, -368, and -390) for its efficacy in reducing the frequency and intensity of menopause-related vasomotor symptoms, and in preventing osteoporosis (loss of bone mineral density). A total of seven dose combinations of FemHRT were investigated in these studies: 0.2/1, 0.5/2.5, 0.5/5, 1/5, 0.5/10, 1/10, and 1/20. No one study had more than 5 of the potential FemHRT doses. Of the 1837 post-menopausal women who entered these studies, 1006 (55%) received at least one dose of FemHRT. The sponsor's Integrated Summary of Effectiveness (ISE) reviewed the efficacy data from the 4 clinical studies. This medical officer review also analyzed the primary data from the in-depth reports of each study. The sponsor is seeking approval of of FemHRT™ NA-EE tablets: 1/5, and

Of the 4 clinical trials, Studies 376-343 and –368 were supportive, but not independently confirmatory of efficacy. Each used inclusion/exclusion criteria and efficacy endpoints that are either unacceptable or not currently recommended. Study 343, for example, had a range of 7-14 subjects per arm and 20% of the enrolled 87 women did not even have vasomotor symptoms at entry. Women were given the choice of taking calcium only, instead of being randomized to a blinded active drug or calcium. Study 368 lasted 16 weeks, assessed hot flash frequency, but not intensity, and had an inclusion criteria of ≥ 20 hot flashes per week in the month prior to enrollment. This latter study, carried out between 7/89 and 12/90 in 219 subjects, did suggest that the lowest dose (0.2 NA/1.0 EE) was not significantly more effective than placebo in treatment of vasomotor symptoms. The remaining 2 trials (-359 and –390) were larger, had more acceptable entry inclusion and exclusion criteria and endpoints, and largely helped to confirm efficacy as discussed earlier in this review.

There is a well-known placebo effect on hot flash frequency and intensity in postmenopausal women. After 12 weeks of treatment, FemHRT, at doses ≥0.2 NA/1.0 EE, was significantly more effective than placebo or calcium-only in reducing hot flash frequency. In addition, FemHRT, at doses of 0.5 NA/2.5 EE to 1 NA/10 EE, was significantly more effective than placebo in reducing hot flash intensity. The effects of the 1/5 and 1/10 FemHRT doses on hot flash frequency were observed within the first 4 weeks and were maintained (in a very small number of women) for up to 5 years. The effects on hot flash intensity were also observed within the first 4 weeks of treatment and were maintained for up to 12 weeks.

Some of the other secondary efficacy parameters studied for all three doses were hot flash frequency/intensity combination scores, "clinical success" (75% improvement over baseline) and 100% elimination rates, and incidence of night sweats. FemHRT was also significantly better than placebo at Week 12 for these secondary endpoints.

The sponsor wanted approval for the indication for treatment of Based on analysis of the limited data provided by studies –343 and –368,

FemHRT, at dosages up to 1 NA/10 EE, protects against endometrial proliferation and hyperplasia when compared with unopposed EE, as indicated by significantly fewer cases of hyperplasia and lower biopsy severity scores. In fact there only one case of questionable endometrial hyperplasia in the 3 FemHRT arms throughout the 24-month study with biopsies being done every 6 months. Review of this case showed that the tissue in question was endocervical squamous metaplasia and that the endometrium was mildly proliferative. The corresponding unopposed estrogen arms showed dose-related endometrial hyperplasia, most notably at the EE 10 mcg level. There was 1 case of hyperplasia with EE 2.5 mcg, 2 cases with EE 5.0, and 9 cases with EE 10.0. The unacceptable high rate of hyperplasia in the 10 mcg ethinyl estradiol arm called for the discontinuation of this dose after 12 months in the large, 24 month 376–359 trial. **It is of note, however, that there was only 1 case of endometrial hyperplasia in the combined 184 evaluable biopsies in unopposed EE 2.5 and 5 mcg subjects at Month 12, and 3 cumulative cases in 157 evaluable biopsies (3%) in unopposed EE 2.5 and 5 mcg subjects at Month 24. This raises the question of the need for any progestin for endometrial protection at these two lower ethinyl estradiol doses.**

One concern is the endometrial protection provided by the FemHRT 1/10 dose compared to 1/5 at Month 12. As shown in the table on page 28, the 1/10 dose had less insufficient tissue biopsies, less atrophic (truly normal for a postmenopausal woman) biopsies, and more proliferative (48% vs. 37%) biopsies. The Month 12, adjusted mean biopsy scores for all three FemHRT groups were approximately the same (~1.45) with the highest score 1.52 for the 1/10 dose, and the lowest score 1.41 for the 1/5 dose. Higher scores correlate with endometrial growth which is less desirable because of the potential risk of hyperplasia and endometrial cancer in postmenopausal women.

The percentage of FemHRT subjects reporting bleeding and/or spotting increases in a dose-related and time-related fashion for the first 12 months. At Month 12, bleeding/spotting was seen in 19% of subjects on FemHRT 0.5/2.5, 24% on 1/5, and 34% on 1/10, compared on only 13% on placebo and 9%, 15%, and 32% in the corresponding unopposed estrogen group. By Month 18, each FemHRT dose has a lower incidence of bleeding/spotting than was seen at Month 12. By Month 24, all three doses have an incidence of bleeding and/or spotting of 10-12%, compared to 6% with EE 2.5 μg alone and 12% with EE 5.0 μg alone. [There was not sufficient data for EE 10 μg because this group was discontinued after Month 12.] The worst bleeding profile was with FemHRT 1/10 with 32 and 34% of subjects reporting bleeding/spotting at Months 6 and 12, 27% at Month 18, and 11% at Month 24. Furthermore, 8 subjects on FemHRT 1/10 withdrew from the study because of bleeding, compared to only 2 on FemHRT 1/5.

9.0 MEDICAL OFFICER OVERVIEW OF SAFETY

A total of 1004 subjects were randomized in the ITT population in the three largest studies (376-359, -368, and –390). Completion rates were comparable and acceptable in the 3 studies as discussed earlier in this review under each study section. From the sponsor's integrated summary of safety (ISS), the most frequent adverse events reported by FemHRT-treated subjects in Studies 376-359, -368, and -390 combined were headache (18%), rhinitis (15%), and breast pain (11%) [see Sponsor Table 20 below]. **Most events did not appear to be dose-related, although headache, nausea and/or vomiting, and breast pain were reported most frequently by subjects in the highest dose FemHRT 1/10 treatment group.**

ISS Table 20. Adverse Events Reported by ≥ 5% of Subjects by Body System[a]
(Studies 376-359, -368, and –390)

BODY SYSTEM/ Adverse Event	Placebo		FemHRT Treatment Groups, NA/μg EE					
			0.5/2.5		1/5*		1/10*	
	N = 247		N = 244		N = 258		N = 255	
BODY AS A WHOLE	99	(40.1)	94	(38.5)	102	(39.5)	112	(43.9)
Headache	36	(14.6)	37	(15.2)	47	(18.2)	52	(20.4)
Back Pain	13	(5.3)	13	(5.3)	12	(4.7)	16	(6.3)
Pain	11	(4.5)	9	(3.7)	10	(3.9)	14	(5.5)
Viral Infection	19	(7.7)	21	(8.6)	18	(7.0)	24	(9.4)
Edema-Generalized	12	(4.9)	12	(4.9)	12	(4.7)	14	(5.5)
DIGESTIVE SYSTEM	44	(24.4)	54	(30.5)	63	(33.0)	68	(35.8)
Nausea and/or Vomiting	13	(5.3)	13	(5.3)	19	(7.4)	23	(9.0)
Abdominal Pain	11	(4.5)	25	(10.2)	21	(8.1)	18	(7.1)
Dental Abnormalities	8	(3.2)	6	(2.5)	12	(4.7)	9	(3.5)
Dyspepsia	5	(2.0)	13	(5.3)	8	(3.1)	9	(3.5)
Diarrhea	9	(3.6)	14	(5.7)	10	(3.9)	11	(4.3)
Flatulence	4	(1.6)	6	(2.5)	6	(2.3)	11	(4.3)
Constipation	10	(4.0)	6	(2.5)	8	(3.1)	13	(5.1)
MUSCULOSKELETAL SYSTEM	39	(21.7)	36	(20.3)	39	(20.4)	39	(20.5)
Arthralgia	17	(6.9)	7	(2.9)	15	(5.8)	9	(3.5)
Myalgia	21	(8.5)	21	(8.6)	20	(7.8)	21	(8.2)
PSYCHOBIOLOGIC FUNCTION	15	(8.3)	14	(7.9)	27	(14.1)	25	(13.2)
Nervousness	4	(1.6)	4	(1.6)	14	(5.4)	7	(2.7)
Depression	9	(3.6)	9	(3.7)	15	(5.8)	15	(5.9)
RESPIRATORY SYSTEM	67	(37.2)	60	(33.9)	68	(35.6)	67	(35.3)
Rhinitis	38	(15.4)	31	(12.7)	39	(15.1)	39	(15.3)
Sinusitis	24	(9.7)	23	(9.4)	21	(8.1)	25	(9.8)
Upper Respiratory Infection	11	(4.5)	10	(4.1)	10	(3.9)	17	(6.7)
Coughing	9	(3.6)	10	(4.1)	9	(3.5)	6	(2.4)
UROGENITAL SYSTEM	45	(25.0)	56	(31.6)	78	(40.8)	79	(41.6)
Breast Pain	13	(5.3)	23	(9.0)	21	(8.1)	43	(16.9)
Urinary Tract Infection	8	(3.2)	9	(3.7)	16	(6.2)	7	(2.7)
Vaginitis	12	(4.9)	11	(4.5)	14	(5.4)	15	(5.9)

[a]The total number of subjects for each body system may be less than the number of subjects with AEs in that body system because a subject may have had > 1 AE per body system.

Medical officer comment: from the above 12-week, 16-week, and 2-year studies with the three doses of FemHRT, all doses were fairly well tolerated by the enrolled healthy postmenopausal population. Three of the symptoms often associated with hormone replacement therapy (headache, nausea/vomiting, and breast pain) were reported by more FemHRT subjects, especially at the highest

dose, than by placebo-treated subjects. The other symptoms higher in FemHRT subjects were abdominal pain, nervousness, and depression. Overall, the majority of these most common AEs reported were mild to moderate in nature, and no clinically important differences were seen between FemHRT and placebo, except for breast pain and nausea & vomiting, in these 1004 women. [Analysis of withdrawals due to AEs follows on page 40.]

Duration of Treatment: the above AEs were summarized by the sponsor by duration of treatment to compare the incidence of AEs in subjects receiving short-term and long-term therapy. AEs in the short-term group were drawn from all 3 studies, whereas AEs in the long-term summary came from Study 376-359, the only study of the three listed with ≥ 20 weeks duration. Hypertension and respiratory system-related events were reported with greater frequency after Week 20, perhaps reflecting the longer time period during which these events might have developed. Breast pain in subjects treated with the highest dose of FemHRT was reported less frequently after Week 20. The frequency of headache and breast pain appeared dose-related when reported on or before Week 15, but not when reported after Week 20.

Medical officer comment: there did not appear to be any clinically important difference in the three FemHRT doses related to the duration of therapy (short-term versus long-term) and compared to placebo.

Deaths: 3 deaths were reported during the clinical trials, all of which occurred during the large 2-year Study 376-359 and which were considered unlikely or definitely not related to study drug. The sponsor table summarizes the three deaths.

Deaths During Study 376-359[a]

Cause of Death	Treatment Group	Subject No.	Relationship to Study Drug
Leiomyosarcoma	Placebo	018-014	Unlikely
Lung Cancer	*FemHRT 0.2/1	009-062	Unlikely
Fractured Cervical Vertebrae	*FemHRT 0.2/1	006-075	Definitely Not

[a] No deaths occurred during Studies 376-343, -368, or –390

* The lowest dose studied and approval is not sought by the sponsor.

Medical officer comment: there were no deaths with any subjects taking one of the three FemHRT doses seeking potential approval. The two deaths that did occur with a dose of NA/EE involved the lowest dose 0.2/1; review of the CRFs showed that neither death was very likely related to the drug.

Serious, nonfatal AEs: in the small, 5-year Study 376-343, 5 serious AEs were reported. Three were breast cancer (2 considered definitely not drug-related and 1 unlikely), one was a DVT considered probably drug-related, and one subject was hospitalized for a rapid heart beat considered definitely not drug-related.

When all and treatment-associated serious adverse event data from Studies 376-359, -368, and -390 were integrated, the following were noted by the sponsor in their ISS (see table below for treatment-associated serious AEs):

- Forty-three FemHRT-treated subjects (5%) reported serious adverse events; 5 (0.5%) reported treatment-associated serious adverse events, listed in the table below;
- There was no apparent dose-related pattern in the frequency of all treatment-associated serious adverse events;
- There were no meaningful differences among FemHRT-treated subjects or between placebo- and FemHRT-treated subjects in the percentage of subjects reporting serious adverse events or in the types of events reported.

Treatment Associated Serious Adverse Events (Studies 376-359, -368, and -390)

Adverse Event	Treatment Group	Number (%) of Subjects	
Migraine	FemHRT 1/5	1	(0.4)
Thrombophlebitis, Deep Vein	FemHRT 1/5	1	(0.4)
Cholecystectomy[a]	FemHRT 1/10	1	(1.0)
Gallbladder Disorder	FemHRT 1/5	1	(0.4)
Breast Mass	FemHRT 0.2/1*	1	(0.5)

[a] After hospitalization for abdominal pain; exact diagnosis not available.

Medical officer comment: the above 5 treatment-associated serious AEs includes only one of the 6 FemHRT treated women (6/1006 FemHRT subjects = 0.6%) who experienced a thromboembolic event. Three women were hospitalized for thromboembolic or phlebitis events as outlined in the table and discussion below. The sponsor felt that two of these three serious AEs were not "treatment-associated," so they were not listed in the above sponsor table.

Thromboembolic Adverse Events: from the four clinical trials, 6 of 1006 FemHRT treated subjects experienced potential thromboembolic events. There were a total of 2 cases of DVT, 2 thrombophlebitis, 1 superficial phlebitis, and 1 possible CVA; three (3/1006 = 0.3%) of these women were hospitalized. The medical officer table below summarizes the 6 cases.

Thromboembolic Adverse Events: ALL FemHRT Subjects (N=1006)

Study	Dose	Event	Age	Days of Rx	Related to study drug*	Associated factors; Complications/recovery
343 (5 year)	1/10	[a]DVT +Doppler & venogram	54	942	Probably	Hx of varicose veins and anemia; recovered well
343	1/20	Thrombophlebitis-superficial	54	39	Not noted	No prior Hx; negative venogram
359 (2 year)	1/5	[b]DVT +Venogram	57	593	Possibly	Smoker; COPD; bed rest x 2 wk prior to Sx
359	1/10	Phlebitis-Superficial, severe	51	509	Probably	None; 21 days to recover
359	0.2/1	[c]Possible CVA; ataxic hemiparesis	61	180	Unlikely	↑BP on admission; Recovered 100%
390 (12 week)	1/5	Thrombophlebitis-superficial, severe	56	40	Possibly	Hx of pyelo ; 96 days to resolve

DVT = deep vein thrombosis; CVA = cerebral vascular accident
*Investigator's opinion
[a]Hospitalized for IV heparin + warfarin; home on tapering schedule of warfarin
[b]Hospitalized for 4 days; treated with warfarin.
[c]Hospitalized; recovered with no further episodes.

Medical officer comment: it is difficult to interpret the clinical significance of the above six cases as there is no common denominator. The dosage in two cases was either the very lowest or highest (1/20 is LoEstrin®, an approved OC). Two were probably and two were possibly related to study drug. Two women were on FemHRT for only their second month, while the others had completed 6, 17, 20, and 31 months of treatment. Only the two women with a documented DVT appeared to have associated risk factors (varicose veins; smoking, COPD and on bed rest). None of the summaries of the six cases provided data concerning known venous thromboembolic event risk factors such as parity, weight, prior history of thromboembolic events, CHF, and OC use. Further analysis by Allen Brinker in the epidemiology branch concluded that "rates of VTE among recent

[FDA-reviewed] clinical trials of HRT were found to be relatively similar and 3 to 5 times higher than seen in observational settings. These relative risks cannot be labeled as clinically or statistically significant as they result from approximations, overlap the background rate, and result from a comparison between observational and RCT data."

Withdrawals: when all withdrawals and withdrawals due to adverse events in Studies 376-359, -368, and -390 were integrated, the following were noted by the sponsor:

- Ninety-seven FemHRT-treated subjects (10%) withdrew due to adverse events; 65 (7%) withdrew due to treatment-associated adverse events;
- Although more FemHRT than placebo-treated subjects withdrew due to treatment-associated adverse events, the events causing withdrawals in FemHRT-treated subjects are common to HRT;
- Although the 2 highest dose groups had more withdrawals (FemHRT 1/5 with 23 and 1/10 with 20) due to adverse events, there was not a true dose-related pattern to these withdrawals; and
- Of the events causing withdrawal, only vaginal hemorrhage (bleeding) and breast pain were dose-related. Depression, although more frequent in the higher FemHRT dose groups, was reported by a comparable percentage of placebo-treated subjects.

Medical officer Table. 5 Most Common AEs Associated with Study Withdrawal (in 3 trials)

Adverse Event	Placebo	FemHRT Treatment Groups, mg NA/mcg EE				Total
	N = 247	0.2/1 N = 184	0.5/2.5 N = 244	1/5 N = 258	1/10 N = 255	N = 1188
Vaginal hemorrhage	1	1	2	4	8	16
Breast pain	1	0	2	3	3	9
Headache	1	1	2	4	1	9
Depression	2	1	1	2	3	9
Weight ⇑	2	1	1	3	0	7
TOTAL	7	4	8	16	15	50

Medical officer comment: five associated AEs categories were the primary reason for withdrawal of 52% (50/97) of the subjects in the three larger studies. They are in order of frequency shown in the medical officer table above. Vaginal hemorrhage and depression appear to be directly dose-related, but the number of withdrawals here is small.

Clinical Laboratory Measurements: the sponsor integrated all apparent dose-related lab test changes from baseline from Studies 376-359, -368, and –390. These lab changes are summarized in the table below. The direction of change in FSH, cholesterol, and SHBG are expected with estrogen use. No FemHRT or placebo treated subject withdrew due to lab abnormalitites nor were any considered to be serious AEs.

Lab Test (units)	Direction of Mean Change	Mean Changes in FemHRT Treatment Groups (mg NA/mcg EE)			
		Placebo	0.5/2.5	1/5	1/10
FSH (mIU/mL)	Decrease	-13	-30	-54	-73
Factor VII (%)	Decrease	-23	-14	-16	-21
Cholesterol (mmol/L)	Decrease	6	-32	-43	-10
Phosphate (mmol/L)	Decrease	-2	-10	-15	-14
Alkaline Phosphatase (U/L)	Decrease	0.5	-10	-15	-16
SHBG (mmol/L)	Increase	5	22	22	51

Medical officer comment: in the 2-year CHART study, the number of changes was not unexpected relative to the size and length of the study and the known effects of estrogens and progestins. There were, however, no clinically significant differences between treatment groups in the frequency of these lab changes. Furthermore, there were no clinically significant dose-dependent changes noted. Although the changes in Factor VII appear to be dose-related, they were less than the decreases seen in the placebo group, and were not clinically significant.

The sponsor reached the following overall eight conclusions:

- No clinically important differences in adverse event experience are seen between FemHRT and placebo/calcium-only treatment.
- Breast pain, edema, headache, and abdominal pain are the most common adverse events associated with FemHRT treatment.
- Three deaths occurred in 1 of the 4 clinical studies; all were considered either unlikely related or unrelated to treatment.
- In general, serious adverse events or withdrawals due to adverse events were either unrelated to or expected with FemHRT.
- No clinically significant differences in clinical laboratory measures are seen between FemHRT and placebo treatment groups.
- No clinically significant dose-dependent changes in any of the clinical laboratory measures are seen in any of the treatment groups.
- In summary, FemHRT is well-tolerated in the subject population studied, with an adverse event profile expected for HRT.

Medical officer comment: I agree that the overall safety profile of FemHRT appears acceptable. The six "thromboembolic AEs" were reviewed and compared to data from other approved HRT products. The two well-documented cases of DVT and three cases of phlebitis are of concern, but are within an acceptable confidence interval. The number of breast cancers is also of concern as noted earlier (page 33).

The common AEs should be reflected in the physician and patient labels for the marketed product.

The medical officer reviewed the Safety Update (Reference No. 003) submitted by the sponsor on April 15, 1999. The report was acceptable and raised no new safety issues.

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10.0 Label History and Issues

The following 16 exchanges with the sponsor and labeling issues are listed chronologically below:

1. August 27: major FDA edits to the proposed label were sent to the sponsor by FAX and secure e-mail
2. August 31: a brief T-con was held informing the sponsor that: 1) [redacted] indication would not be allowed because the studies had inadequate data to support this indication; and 2) some statement would be required in the label concerning the [redacted]
3. September 2: the sponsor called project manager D. Moore about their request to leave the chemistry portion of the product name as NA/EE, instead of our recommended EE /NA. All other currently approved drugs for hormone replacement therapy list the estrogen first, followed by the progestin.
4. September 7: project manager was informed that the sponsor wants [redacted]
5. September 9: hard copy of the sponsor's response to the FDA-recommended label changes was provided to the DRUDP
6. September 10: 1-hour T-con with sponsor concerning label changes. Major clinical issues discussed and conclusions reached were:
   - Sponsor may keep the order of active ingredients as NA/EE ; this will be the first HRT product with the progestin listed before the estrogen, which may be confusing to the prescribing doctor, HCP or pharmacist
   - Concerning endometrial hyperplasia data, the label may delete [redacted] and add Month 24 data
   - The indication for management of osteoporosis will not be allowed because the sponsor did not specifically study this; prevention of osteoporosis will be allowed provided it is approved by DMEDP
   - The indication for treatment of [redacted] needs conclusive data including maturation indices; the medical officer could not find this data in the submission and was concerned that only 14 women in each dose group would have had this lab parameter performed. Comparison to placebo will need to be made.
   - Concerning [redacted] the FDA felt that including mean changes in any ratios is not meaningful and should not be included. Sponsor will not include [redacted]
7. September 17: T-con with sponsor; major points agreed on:
   - Cumulative amenorrhea rates should be shown for 12 months or longer
   - Quality of Life statements will be reviewed by the FDA DDMAC division
   - An indication for treatment of [redacted] will not be granted
   - Protection of the Endometrium is not an indication; it is a valid safety concern and data should be reflected in the label
   - No specific reference will be made to [redacted] in the PK section on absorption and bioavailability
   - [redacted] will be deleted
8. September 17 T-con: major points to be further discussed
   - the exact labeling for the osteoporosis prevention indication
   - the patient label
9. September 29 T-con: major points presented
   - the sponsor was informed for the first time by Dr. Rarick that the trade name FemHRT was not acceptable to the LNC because of two products Femstat and [redacted] with similar names
   - Sponsor notified that the FemHRT [redacted]
   - Other minor changes in the MD label were outlined in detail
10. October 4 meeting with DRUDP and DDMAC
    - Entire MD label reviewed and edited
    - [redacted] will need to be deleted by the sponsor

- Statement about [redacted] should be deleted
- [redacted] section should be deleted
- Karen Lechter from DDMAC will edit the patient package insert for readability

11. October 4 internal meeting at division and office level with DRUDP and DMEDP
    - Trade name femhrt discussed and proposed by both divisions
    - Agree that [redacted]
    - Agree that 1/5 dose will be approved for VMS and osteoporosis prevention
    - [redacted]
12. October 8 consult by OPDRA:
    - recommends the use of the phonetic spelling in conjunction with approved proprietary and generic names as well as pending names;
    - conducted a small survey that found 7/13 people pronounced the name as "femheart;"
    - felt there was a definite potential risk of cardiac promotional claims on behalf of the sponsor
13. October 8 T-con with the sponsor
    - Trade name of femhrt (pronounced fem irt or fem hert) is acceptable
    - The only dose to be approved for vasomotor symptoms and osteoporosis prevention is femhrt 1/5; the [redacted] Thus, femhrt 1/5 is the lowest dose that is effective and safe for the VMS and osteoporosis indications.
    - Our division comments from 10/4 concerning the physician label were discussed; there was still disagreement over the following issues:
      - [redacted]
    - Patient package insert (PPI) was sent to sponsor by secure e-mail
    - Sponsor will send our division further information concerning femhrt as soon as possible
14. [redacted]
15. October 13 T-con with Ross Lobell: edits for the final physician label discussed and agreed upon
16. October 14 T-con with the sponsor: edits for the final patient package insert (PPI) agreed upon

Label negotiations took longer than normal because of the sponsor's reluctance to accept the FDA rejection of the trade name FemHRT and the FDA's recommended [redacted] Further disagreement centered on the FDA position to exclude [redacted] Both FDA divisions were willing to approve and include the [redacted] but the sponsor did not want to because of their problems related to [redacted] The FDA did recommend that the estrogen should be listed first, followed by the progestin (as is true with all other HRT approved products), but did agree to allow the reverse order (namely, progestin/estrogen) in the final approved name femhrt NA/EE.

APPEARS THIS WAY
ON ORIGINAL

11.0 MEDICAL OFFICER SPECIAL CONCERNS

There were two issues that were of special concern to the medical officer. First is the questioning of the need for norethindrone acetate for endometrial hyperplasia protection and the [redacted] Second is the official trade name of the approved product, listing the progestin first, followed by the estrogen (e.g., FemHRT 1/5 versus FemHRT 5/1), and the use of the name, FemHRT, itself.

Endometrial protection: Concerning endometrial hyperplasia in the unopposed 2.5 mcg ethinyl estradiol group, there were no cases (0/90 evaluable biopsies) at Month 12, and only one case (1/67) at Month 24. Likewise, in the unopposed 5.0 ethinyl estradiol group, there was one case (1/94 evaluable biopsies) at Month 12, and one additional case (1/90) at Month 24. So the overall incidence of endometrial hyperplasia was very low (1 and 2%, respectively) in the 2.5 and 5.0 mcg unopposed ethinyl estradiol groups. One might question the need for any additional progestin for endometrial protection at these lower ethinyl estradiol doses. In the FemHRT 0.5/2.5 and 1/5 groups, there were no cases of endometrial hyperplasia at Months 12 and 24. Evidence for the "protective" effect of the norethindrone acetate is clearer when the percentage of biopsies in the two groups are compared for atrophic vs. normal proliferative tissue. The unopposed 2.5 mcg ethinyl estradiol group had 13% (21/157) atrophic biopsies compared to FemHRT 0.5/2.5 with 56% (71/126). The 5.0 ethinyl estradiol group had 2% (4/184) atrophic biopsies compared to FemHRT 1/5 with 57% (74/130). Conversely, the percentage of biopsies with proliferative changes was much higher in the two unopposed ethinyl estradiol arms compared to the corresponding FemHRT arms. The addition of 0.5 or 1.0 mg NA protects against both endometrial hyperplasia and endometrial proliferation at the lower 2.5 and 5.0 mcg ethinyl estradiol doses. Furthermore, it raises no safety concerns, so its overall benefit outweighs its risks.

[redacted]

Trade Name: All currently approved products (oral and transdermal) for hormone replacement therapy list the estrogen first and the progestin second in their trade name. So up to this point in time, health care providers have been accustomed to this sequence. The sponsor has other norethindrone acetate/ethinyl estradiol products on the market, such as LoEstrin 1/20 and 1.5/30, but they are for contraception where all other FDA-approved combination products list the progestin first. The sponsor prefers to keep the same progestin/estrogen sequence in the FemHRT name. This will be allowed, but a word of caution is appropriate. The sponsor should be very careful that both prescribers and consumers do not, for example, confuse the 5.0 mcg EE with 5.0 mg medroxyprogesterone, or the 1 mg NA with 1mg E_2, due to the reversing of the estrogen/progestin order in the trade name.

Another concern, discovered late in the review process, is the Label and Nomenclature Committee decision that the name FemHRT is not acceptable because there are two other marketed products, Femstat and [redacted] with similar names. Furthermore, there is concern that FemHRT will be pronounced "fem heart,"

implying that the product is beneficial for the heart when there is no data from the clinical trials supporting this claim. The sponsor was informed of this on September 29, 1999. Further resolution of this issue resulted in a compromise name of femhrt, to be pronounced "fem irt" or "fem hert." OPDRA was consulted and was still concerned that the name had the potential risk of cardiac promotional claims. The sponsor was warned about this as a potential future issue.

12.0 Final Medical Officer Recommendations

The sponsor has submitted in this NDA data from two supportive and two pivotal clinical trials. In women with an intact uterus, the following recommendations are made for femhrt in the [redacted] 1 mg NA/5.0 µg EE, and [redacted]

- For the treatment of moderate to severe vasomotor symptoms associated with the menopause in women with an intact uterus:
  - Approval of femhrt [redacted] 1/5
    - [redacted]

- For the safety concern of demonstrating adequate endometrial hyperplasia protection
  - Approval of only femhrt [redacted] 1/5

- Approval for the agreed-upon trade name "femhrt" listing the progestin first and the estrogen second. The sponsor should take special precaution to alert prescribers (healthcare providers), dispensing agents (pharmacies and clinics), and consumers to the reversal of the order of active ingredients compared to all other currently approved hormone replacement therapy products

- the lowest dose and regimen that will control symptoms should be prescribed;
  - postmenopausal women on femhrt should reevaluate every 3 to 6 months with their healthcare provider to determine whether or not the medication is still needed for control of vasomotor symptoms

Decisions concerning the prevention of osteoporosis and the corresponding labeling will be made by the Division of Endocrine and Metabolic Drug Products in a separate review.

[redacted]

/S/ 10/14/99

Daniel Davis, MD, MPH
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DRUDP

/S/ 10/14/99

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cc: Rarick/ Spellissane/ Hoberman/ Ortwerth/ Jarugula
Zawadzki/ Gaulliers / Trendle/ Sobel
Division files, DRUDP and DMEDP