CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-102

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-102

1 General Information

1.1 NDA 21-102 This is a Type 6 NDA for the osteoporosis indication, which has been submitted as NDA 21-065 in HFD 580 for hormonal replacement therapy in postmenopausal women with an intact uterus.

1.2 Applicant: Parke-Davis
Division of Warner-Lambert Company
2800 Plymouth Rd.
P.O. Box 1047
Ann Arbor MI 48106-1047

Contact: Mary E. Taylor, M.P.H.
Director, Worldwide Regulatory Affairs
734- 622-5000

1.3 Submission/review dates

1.3.1	Date of Submission:	12/16/98
1.3.2	CDER (HFD-580) stamp date:	12/17/98
1.3.3	Date submission received (HFD-510):	1/26/99
1.3.4	Date review completed:	10/3/99; updated 10/7/99

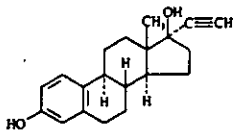
1.4 Drug Identification

1.4.1 Generic name: norethindrone acetate (USP) and ethinyl estradiol (USP) [abbreviated as NA/EE]

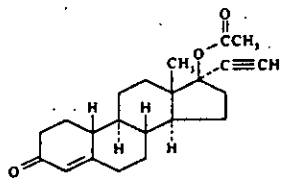
1.4.2 Proposed trade name: FemHRT

1.4.3 Chemical name: (17alpha)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol and (17alpha)-17-(acetyloxy)-19-norpregn-4-en-20-yn-one

1.4.4 Chemical structure:



Ethinyl Estradiol



Norethindrone Acetate

APPEARS THIS WAY
ON ORIGINAL

1.4.5 Molecular formula: $C_{22}H_{28}O_3$ (norethindrone acetate) and $C_{20}H_{24}O_2$ (ethinyl estradiol) in a 1:1 ratio

1.4.6 Molecular weight: 636.87 (for combined product); norethindrone acetate 340.7; ethinyl estradiol 296.41

1.5 Pharmacologic Category: Combination Product of Progestagen and Estrogen

1.6 Dosage form: Approval of the [redacted] 1/5, [redacted] mg norethindrone acetate (NA) / mcg ethinyl estradiol (EE) is sought by the sponsor in the NDA; in a teleconference with HFD-580 in early September 1999, the sponsor requested withdrawal of the [redacted] mgNA/mcgEE dosage from the label because of a [redacted] The [redacted] was formally withdrawn in writing on 9/28/99

1.7 Route of Administration: oral

1.8 Proposed Indication and Usage : Prevention of Postmenopausal Osteoporosis (Treatment of Vasomotor Symptoms Indication is being reviewed in HFD-580 NDA 21065)

1.9 Proposed Dosage and Administration:
as of early September 1999, the sponsor wishes to market only the 1/5 and [redacted] mgNA/mcgEE oral dosage forms

1.10 Related Drugs: conjugated (oral) estrogens; transdermal estradiol; 1/20 mgNA/mcgEE (Loestrin- marketed by Parke-Davis for oral contraception [approved NDA 17-876])

1.11 Material Reviewed: NDA 21-102 volumes 1, 2, 3, 22, 49-54, 69-72, 77-98, 110-112, electronic case report forms

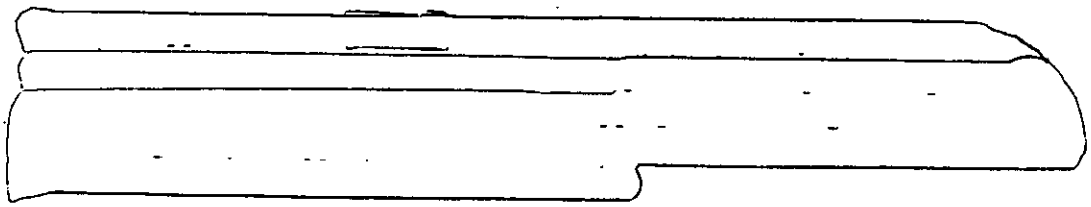
1.12 Regulatory Background
FDA meetings: End-of-Phase 2 (7/12/1988)
Meetings to discuss study design and handling of cases of endometrial hyperplasia: 2/17/89, 7/20/89, 12/7/90, 8/2/91, 8/6/92
Pre-NDA Meetings: 9/22/92, 6/3/96
Related INDs: IND [redacted] and [redacted]

This review has been discussed with the statistical team, David Hoberman, Ph.D. and Todd Sahlroot, Ph.D., statistics team leader, and the Division of Reproductive and Urologic Drug Products.

Regulatory Recommendation:

Approval of the 1/5 norethindrone acetate ethinyl estradiol (mgNA/mcgE)dosage for the indication of prevention of postmenopausal osteoporosis in women with intact uteri, pending

1) adequate final sponsor responses to FDA questions;
2) change in labeling, as requested by FDA.



APPEARS THIS WAY
ON ORIGINAL

Abbreviations are defined in the text and also below:
AE=adverse events; **BMD**=bone mineral density; **EE**=ethinyl estradiol; **LOCF**=last observation carried forward or endpoint, referring to statistical analysis; **mg/cm^3=mg/cc** used as measure of bone mineral density measured by quantitative computerized tomography; **MPA/CEE**=medroxyprogesterone acetate/conjugated equine estrogen; **NA/EE** = norethindrone acetate ethinyl estradiol; **NDA**=New Drug Application; **QCT**=quantitative computerized tomography for assessment of bone mineral density; **RCT**=randomized clinical trial; **SHBG**=sex hormone binding globulin.

APPEARS THIS WAY
ON ORIGINAL

2 Table of Contents - Medical Officer's Review of NDA 21102

Summary

The NDAs 21065 (in HFD-580) and 21102(in HFD-510) are one application for a fixed combination of norethindrone acetate (NA) and ethinyl estradiol (EE) in dosages 1/5, and mg NA/mcgEE daily for continuous combined hormone replacement therapy for postmenopausal women with intact uteri. These NDAs have been simultaneously reviewed in the Division of Reproductive and Urologic Drug Products (HFD-580) and Division of Endocrine and Metabolic Drug Products (HFD-510) for the following indications, respectively: treatment of moderate to severe vasomotor symptoms associated with menopause (HFD-580 – Dan Davis, M.D., medical reviewer) and prevention of osteoporosis (HFD-510 – this review) in postmenopausal women with intact uteri.

The rationale for a combined progestagen/estrogen drug product is the provision of estrogen protective effects with protection from endometrial hyperplasia. The specific combination NA EE has been marketed for contraception with higher EE doses for the past 30 years to an estimated 60 million women worldwide. Neither EE nor the combination NA/EE have been previously approved for osteoporosis in the United States.

3. Chemistry/Manufacturing Controls

Both active ingredients, norethindrone acetate (USP) and ethinyl estradiol (USP), are official compendial items, which are tested according to the methods and specifications described in the respective current compendia monographs. The NDA refers to the manufacturer's Drug Master Files. The supplier is and the manufacturer is Duramed Pharmaceuticals Inc. is responsible for the testing, approval, and release of the drug substances and for manufacturing, packaging, and labeling of the drug product. The marketed drug product is to be provided in different shapes D shape, for the different strengths mgNA/mcgEE 1/5, respectively. Inactive ingredients in the drug product and include lactose monohydrate, corn starch, microcrytalline cellulose, calcium stearate.

4. Animal Pharmacology/Toxicology

No animal pharmacology/toxicology data are submitted.

5. Microbiology

No microbiology studies were submitted.

6. Human Pharmacokinetics/Pharmacodynamics

Norethindrone acetate (NA) is rapidly and completely deacetylated to norethindrone (N) after oral administration. NA is rapidly absorbed with peak plasma concentration within 2 hours after dosing. Ethinyl estradiol (EE) is also rapidly absorbed, with peak plasma concentrations 1-2 hours after oral administration. Both NA and EE are subject to first-pass metabolism with oral availability 64% (47-73%) and 55% (24-99%) respectively. In the presence of food, N and EE

Cmax were decreased 12 and 29%, respectively, and the tmax value was increased from 1.6 to 2.5 and 3.7 hours, respectively. However, the randomized clinical trials were conducted with no restrictions relative to food. Plasma protein binding of both steroids exceeds 95% (N to both albumin and sex hormone binding globulin (SHBG), whereas EE binds only to albumin. However , EE induces SHBG synthesis and NA/EE increases SHBG values approximately 2.6 fold over baseline. EE is extensively metabolized, both by oxidation to 2-hydroxy EE formed by the CYP3A4 isoform of cytochrome P450, and conjugation with sulfate (major circulating conjugate) and glucuronide (which predominates in urine). Part of the first-pass metabolism may occur in gastrointestinal mucosa and may undergo enterohepatic circulation. NA also undergoes sulfate and glucuronide conjugation. **Of note, a small amount of NA is metabolically converted to EE, so that 1mg NA administration equals 2.8 mcgEE.** Plasma clearance for both NA and EE is approximately 0.4 L/hr/kg; steady state elimination half-lives of N and EE are 13 and 24 hours, respectively.

Both N and EE are excreted in urine and feces, primarily as metabolites, however effect of renal disease on NA/EE disposition has not been studied. No effect of age has been observed in N and EE pharmacokinetics in premenopausal and postmenopausal women. Effect of hepatic disease on disposition of N and EE has not been studied, though N and EE may be poorly metabolized in women with impaired liver function as they are extensively metabolized.

From literature data about NA, N, EE in oral contraceptives, information regarding drug-drug interactions is summarized in the NDA. No drug-drug interactions were conducted with FemHRT. The metabolism of N and EE is increased by a number of drugs, including rifampin, anticonvulsants, troglitazone, and possibly antibiotics (such as ampicillin, tetracycline, griseofulvin) and lower plasma concentrations of N and EE have been observed in many of these situations. Conversely, atorvastatin, fluconazole, ascorbic acid, and acetaminophen may increase plasma EE concentrations, possibly by inhibition of metabolism. In addition, EE may inhibit metabolism of cyclosporine, prednisolone, and theophylline, with resulting increased concentrations of these products.

The market-image drug product is a different preparation from the clinical trial drug product, but bioavailability of these drug products is reported as equivalent, except for a [redacted] from the market image[redacted]

7. Human Clinical Experience

7.1 Foreign Experience: There is no prior foreign marketing experience for FemHRT, as this preparation has not been marketed..

7.2 Post-Marketing Experience

The specific strengths of NA/EE have not been previously marketed.

8. Clinical Studies

The clinical pharmacology and the clinical studies are listed in the sponsor's tables below. The 4 clinical studies were:

- 376-343, a 5-year study, one year partially blinded and four years open label,compared 5 dose combinations of norethindrone acetate/ethinyl estradiol with cyclic MPA/CEE or calcium-only;
- 376-359, the largest of the 4 clinical studies, was a 2-year, placebo-controlled investigation of 4 dose combinations of norethindrone acetate/ethinyl estradiol and 4 doses of EE versus placebo;
- 376-368, a 16-week, placebo-controlled study, examined 4 dose combinations of norethindrone acetate/ethinyl estradiol and placebo; and
- 376-390, a 12-week, placebo-controlled study, compared 3 dose combinations of norethindrone acetate/ethinyl estradiol with placebo.

TABLE 1. Clinical Pharmacology Studies

Study Number	Study Design	Number of Subjects[a]	Demographics	Inclusion Criteria	Drugs, Strengths, Dosage Forms (mg NA/μg EE)	Dosing Regimen	NDA Location Vol	NDA Location Page
376-377	Nonblind, randomized, single-dose, 3-way crossover	26	Mean age, yr 48 (27-62) Race White: 25 (96%) Other: 1 (4%)	Women 21-65 yr, total hysterectomy	1/5 tablet, clinical lot and MI lot; 15 mg NA +75 □g EE in liquid from MI lot	Single doses of 15 1/5 clinical lot; MI tablets; and 15 mg NA +75 □g EE in liquid from MI lot	54	2
376-391	Nonblind, single- and multiple-dose	18	Mean age, yr 57 (50-70) Race White: 18 (100%)	Women 50-70 yr, postmenopausal > 1 yr, FSH >40 mIU/mL, and estradiol <20 pg/mL	1/10 tablet, clinical lot	One 1/10 tablet QAM on Day 1 and on Days 3 through 87	55	1
376-392	Nonblind, randomized, single-dose, 2-way crossover	36	Mean age, yr 58.75 (51-70) Race White: 36 (100%)	Women 50-70 yr, Postmenopausal >1 yr, FSH >40 mIU/mL, and Estradiol <20 pg/mL	0.5/2.5 tablet, clinical lot and MI lot	Single doses of 6 0.5/2.5 clinical lot and MI tablets	56	1
376-393	Nonblind, randomized, single-dose, 2-way crossover	36	Mean age, yr 58.8 (50-70) Race White: 36 (100%)	Women 50-70 yr, postmenopausal >1 yr, FSH >40 mIU/mL, and estradiol <20 pg/mL	1/5 tablet, clinical lot and MI lot	Single doses of 3 1/5 clinical lot and MI tablets	57	1
376-394	Nonblind, randomized, single-dose, 2-way crossover	36	Mean age, yr 61.0 (50-70) Race White: 36 (100%)	Women 50-70 yr, postmenopausal >1 yr, FSH >40 mIU/mL, and estradiol <20 pg/mL	1/10 tablet, clinical lot and MI lot	Single doses of 2 1/10 clinical lot and MI tablets	58	1
376-395	Nonblind, randomized, single-dose, 3-way crossover	18	Mean age, yr 58.7 (51-70) Race White: 18 (100%)	Women 50-70 yr, postmenopausal >1 yr, FSH >40 mIU/mL, and estradiol <20 pg/mL	1/10 tablet, MI; 2 mg/20 μg hydro-alcoholic solution	Single doses of: 2 1/10 MI tablets while fasting; 2 1/10 MI tablets with food; and 2 mg NA/plus 20 μg EE hydroalcoholic solution while fasting	59	1
376-396	Nonblind, randomized, single-dose, 3-way crossover	18	Mean age, yr 58.1 (50-68) Race White: 18 (100%)	Women 50-70 yr, postmenopausal >1 yr, FSH >40 mIU/mL, and estradiol <20 pg/mL	0/10, 1/0, and 1/10 hydroalcoholic solution	Single doses of 1 mg NA hydroalcoholic solution; 10 μg EE hydroalcoholic solution; and 1 mg NA/10 μg EE hydroalcoholic solution	60	1

NA/EE = Norethindrone acetate (mg)/ethinyl estradiol (μg); EE = Ethinyl estradiol (μg); MI = Market-image

[a] All subjects received either FemHRT market-image tablets, FemHRT clinical lot tablets, and/or NA/EE in a hydroalcoholic solution.

APPEARS THIS WAY
ON ORIGINAL

TABLE 2. Clinical Studies

Study Number	Study Design	Number of Subjects (FemHRT)	Demographics	Inclusion Criteria	Daily Treatment & Regimen	NDA Location	
						Vol	Page
376-343	1-year, active-controlled, partially blinded, parallel-group, pilot dose-response, single center with 4-year, open-label extension (7/85-6/91)	87 (65)	Mean age, yr 53 (37-59) Race White: 87(100%)	Nonsmoking white and Asian women, naturally or surgically (bilateral oophorectomy) menopausal ≤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 QD. All groups also received Calcium 1000 mg in divided doses.	69-72	1
376-359	2-year, randomized, double-blind, placebo-controlled, parallel-group, multicenter (7/89-8/93)	1265 (566)	Mean Age, yr 52 (40-64) Race White: 1202 (95%) Black: 16 (1%) Other: 47 (4%)	Women ≥40 years of age with intact uteri; naturally menopausal (E_2 ≤40 pg/mL and FSH ≥40 mIU/mL) ≤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 QD. All groups also received Calcium 1000 mg in divided doses.	77-98	1
376-368	16-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter (7/89-12/90)	219 (176)	Mean age, yr 52 (41-65) Race White: 200 (91%) Black: 16 (7%) Other: 3 (1%)	Women ≥40 years of age with intact uteri, naturally menopausal (E_2 ≤40 pg/mL and FSH ≥40 mIU/mL) ≤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 QD	73-76	1
376-390	12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter (3/96-4/97)	266 (199)	Mean age, yr 51 (40-62) Race White: 239 (90%) Black: 14 (5%) Other: 13 (5%)	Women ≥40 years of age with intact uteri, naturally or surgically menopausal ≤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 QD	101-107	1

MPA/CEE = mg Medroxyprogesterone acetate/mg conjugated equine estrogen; FSH = Follicle-stimulating hormone.

[a] After 1 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.

APPEARS THIS WAY
ON ORIGINAL

TABLE 3. Clinical Studies: Source and Number of Subjects[a]

Study	Placebo	FemHRT Treatment Groups, mg NA/μg EE							MPA/CEE mg/mg	EE (μg)				Total
		0.2/1	0.5/2.5	0.5/5	1/5	0.5/10	1/10	1/20	10/0.625	1	2.5	5	10	
376-343[b]	10	--	--	12	14	13	14	12	12	--	--	--	--	87
376-359[b]	137	139	136	--	146	--	145	--	--	141	137	141	143	1265
376-368	43	45	41	--	45	--	45	--	--	--	--	--	--	219
376-390	67	--	67	--	67	--	65	--	--	--	--	--	--	266
Total	257[c]	184	244	12	272	13	269	12[d]	12	141	137	141	143	1837

-- = Not applicable.

[a] Totals are numbers of subjects at baseline of each study.

[b] All subjects received 1000 mg calcium daily in divided doses.

[c] Includes 10 subjects taking only calcium in Study 376-343

[d] Subjects were reassigned after Month 12 to the following FemHRT treatment groups: 2 to 0.5/2.5, 3 to 1/5, 3 to 0.5/10, and 3 to 1/10. One subject chose not to continue in the study.

8.1 Introduction

The efficacy and safety of norethindrone acetate ethinyl estradiol (NA/EE or FemHRT) has been assessed in 4 clinical trials, with a total of 1837 subjects enrolled: 1006 were exposed to one of 7 strengths of NA/EE (0.2/1, 0.5/2.5, 0.5/5, 1/5, 0.5/10, 1/10, 1/20); 574 were treated with unopposed EE or medroxyprogesterone acetate/conjugated equine estrogen (MPA/CEE); 257 were treated with placebo or calcium only. Two studies (376-368 and 376-390) assessed hot flash frequency and intensity and were 12-16 weeks in duration. Two studies (376-343 and 376-359) assessed endometrial protection and bone mineral density. The studies that assessed bone mineral density are listed and discussed below. The other studies are reviewed in HFD-580. In addition 7 clinical pharmacology studies enrolled 188 naturally or surgically postmenopausal healthy women, exposing 36, 54, 72, and 26 subjects to single doses of 1/10, 2/20, 3/15, and 15/75 mgNA/mcgEE.

Fem HRT bone density studies (adapted from Table 6, ISS, p.25 of 86)

Study number	Study design	# Subjects (FemHRT)	Primary Endpoints	Inclusion Criteria	Treatment
376-343	1 year, randomized, active controlled, partially blinded, parallel group, pilot dose response, single center with 4yr open label	87 (65)	Lumbar spine BMD, hot flash frequency, endometrial effects	Nonsmoking white & Asian women, naturally or surgically (bilat. Oophorectomy) menopausal ≤ 5 yrs; no hormone use for 3 mths prior to study entry; open label study required completion of 1 yr phase	NA/EE 0.5/5, 1/5, 0.5/10, 1/10, 1/20[a] or MPA/CEE 10/0.625 qd or placebo; All received 1000 mg calcium in divided doses
376-359	2-yr, RCT, double blind, placebo controlled, parallel group, multicenter	1265 (566)	BMD and endometrial effects	Postmenopausal (≤ 5yrs) women ≥ 40 years of age with intact uteri; lumbar spine trabecular BMD 90-160 mg/cm; no hormone or calcitonin use within 6 months of study entry	NA/EE 0.2/1, 0.5/2.5, 1/5, 1/10, or EE 1, 2.5, 5, 10[b], or placebo qd; all received 1000 mg calcium in divided doses

[a] After one year, subjects in the 1-mg NA/20mcg EE dosage group were randomly reassigned among the remaining NA/EE dosage groups.
[b] The 10 mcg EE dosage group was discontinued early due to a rate of endometrial hyperplasia that exceeded the protocol-specified level.

Study **376-343** was a small single-center study. A total of 87 postmenopausal women ≤ 5 years postmenopausal prior to study start were randomized to a calcium placebo group, an active MPA/CEE comparison arm, or to 5 dosage combinations of NA/EE (0.5/5, 1/5, .5/10, 1/10, 1/20 mg NA/mcgEE) for 1 year. Only the women in the NAEE were administered double-blind

medications. Subjects remained in initial treatment groups for the 4 open-label extension period. Since data from the 1 year phase revealed that doses lower than 1/20 mgNA/mcgEE provided adequate relief of menopausal symptoms with less vaginal bleeding, women from the 1/20 group were re-randomized to the other treatment groups.

Primary efficacy parameters for this study included reduction in hot flash frequency, prevention of endometrial proliferation and hyperplasia, prevention of BMD loss as measured by quantitative computerized tomography (QCT).

Secondary efficacy parameters included biochemical markers of bone – serum total alkaline phosphatase, urinary hydroxyproline:creatinine ratio, and urinary calcium.

The primary analysis was an intent-to-treat analysis of all subjects with data during the specified time interval. Changes in BMD were evaluated by calculating the mean change from baseline at each yearly followup visit using ANCOVA with baseline bone density as covariate. 95% confidence intervals were calculated for the difference in mean change from baseline between the calcium only treatment group and all hormonal treatment groups. Dunnett's test was used to compare each hormone only treatment group to the calcium only treatment group.

87 postmenopausal women were enrolled: 9(90%), 56 (86%), 8 (67%) completed the one year calcium, NA/EE and MPA/CEE arms respectively. 5, 53, and 4 of these 1 year completers entered the 4-year open-label study and 5 (50%), 42 (65%), and 1 (8%) completed the total 5-year study. The ANCOVA-adjusted mean change in BMD (mg/cm^3) at one year was 3.1 for the calcium group, 10.1, 9.2, 8.9, 16.2, 16.8 for the 0.5/5, 1/5, .5/10, 1/10, 1/20 mg NA/mcgEE, and 14.9 mg/cm^3 for the 10/0.625 MPA/CEE ($p=0.03$). At year 5, this ANCOVA-adjusted mean change in BMD was –10.2 for the calcium, 2.0, -0.1, 0.1, 5.9 mg/cm^3 for the NA/EE ($p=0.19$). Biochemical bone marker trends paralleled the BMD data. Alkaline phosphatase levels did not change in the calcium only treatment group and tended to decrease in hormonally treated women as BMD increased. Hydroxyproline:creatinine ratios initially decreased in year 1 in hormone and calcium-treated subjects and then by the end of year 2 were higher than at baseline. Urinary calcium increased in calcium-treated and hormonally treated subjects initially, which may reflect adjustment to calcium supplementation. Hormonal replacement may have reduced bone turnover in the second year, as suggested by the decrease in calcium excretion.

Reviewer's Comment: The small, single-center randomized population in this study and the small percentage of completers make it difficult to extrapolate conclusions. This study was essentially a preliminary dose ranging study for study 376-359.

The **study 376-359** is the main focus of this review as it is a large, multicenter, double blind placebo-controlled randomized clinical trial (RCT). The sponsor refers to this trial as CHART (continuous hormones as replacement therapy). Subsequent referral to this trial will be as RCT, as it is the only double-blind RCT for this indication.

8.2 Indication: Prevention of Postmenopausal Osteoporosis in Postmenopausal Women with Intact Uteri

8.2.1 Objective/Rationale

The main objectives of study 376-359 were the following:
(1) to demonstrate the protective effect on the endometrium of continuous administration of NA/EE compared to corresponding doses of unopposed EE;
(2) to compare the efficacy of 4 dose combinations of NA/EE (0.2/1, 0.5/2.5, 1/5, 1/10 mg NA/mcg EE) with that of placebo in preventing decrease in bone mineral density;
(3) to assess the safety of continuous administration of the 4 dose combinations of NA/EE.

Part of this safety assessment included the evaluation of changes in selected lipid parameters, as a potential risk of progestin therapy is the reversal of positive effects of estrogen on serum lipids.

Estrogen deficiency postmenopausally is associated with vasomotor symptoms, symptoms associated with genital atrophy, and increased risk of osteoporosis. Estrogen replacement therapy attenuates the symptoms of menopause and prevents decrease in bone mineral density, but unopposed exogenous estrogen administration has been associated with development of endometrial hyperplasia in 12 – 32% of patients. The addition of a progestogen to cyclic estrogen regimens has been associated with reduction of the risk of estrogen-induced hyperplasia to 0-2% and some reversal of the positive effects of estrogen on serum lipids. In the PEPI trial, for example, a 3-year, multicenter, randomized, double-blind, placebo-controlled trial of 875 healthy postmenopausal women, combined estrogen-progestogen therapy (cyclic or continuous) resulted in a lower incidence of simple (0.8 versus 27.7%), complex (0.8 versus 23.7%), and atypical hyperplastic (0 versus 11.8%) lesions than estrogen therapy alone. [The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. JAMA 1996; 275: 370]

8.2.2 Study Design

The study 376-359 is a large, multicenter, double blind, placebo-controlled, parallel-group, randomized clinical trial (RCT). 65 centers participated in this study; an additional 18 centers were withdrawn or closed during the enrollment stage of the study due to lack of patients. A total of 1265 postmenopausal women were randomized. The numbers of patients randomized ranged from 1-39 per center and the number of patients completing ranged from 0-30 per center; thus, the number of completers per center ranged 0-83% (note: the 30 completers refer to a center where 36 patients were randomized). The study was conducted between 7/26/89 (first patient enrollment) and 8/15/93 (last patient completion).

After a 30-day screening, patients were randomly assigned to 1 of 9 treatment groups for a 24-month double-blind treatment period: placebo, 0.2/1, 0.5/2.5, 1/5, 1/10 mg NA/mcg EE, and 1, 2.5, 5, and 10 mcg EE. In addition all patients received 1000 mg calcium daily. Patients in the 10 mcg EE treatment group were discontinued midway through the study because of an unacceptably high rate of endometrial hyperplasia, as required for safety reasons in the protocol.

8.2.3 Protocol Overview

In the protocol, sample size was calculated separately for the endpoints of endometrial hyperplasia and bone loss. For bone density, the mean of 130 mg/cm ^{3} and variance of 225 were estimated using all patients in Protocol 376-343 pilot study (Research Report 940-00115) with a bone density between 160 (which was amended from 150 on 7/30/90) mg/cm^3 and 90 mg/cm^3. The study was powered at 0.095 to detect a 3% loss in bone density per year over two years and a sample size of 100 per treatment group was required for a significance level of 0.05. The sample size of 110 per treatment group for endometrial hyperplasia was calculated on the basis of a significance level of 0.045 (0.005 was spent on the one year interim test) and power of 0.95 assuming a hyperplasia rate of 12% in unopposed EE groups and 1% in the combination groups in the second year. As a safety consideration, any treatment group with a rate of hyperplasia that exceeded twice the concurrent rate in the placebo or 6%, whichever is higher, would be terminated. A rate of 3% was expected for the untreated population. After the data collection was completed, criteria for the exclusion of bone mineral density from the evaluable analysis (years 1 and 2) were established. (11/29/93) The sponsor presents this evaluable analysis as the primary analysis.

Reviewer's comments: The evaluable analysis is essentially a *post hoc* analysis. The FDA emphasizes the intent-to-treat analysis, which was considered the primary analysis in this review. The data from the evaluable analysis were compared to the intent-to-treat analysis.

8.2.3.1 Population, procedures

The patient population in the RCT comprised 1265 healthy, non-osteoporotic, postmenopausal women, with an intact uterus. The majority of the study population were Caucasian (95%) with a mean age of 52 years. 96 (67%) were active in the 10 mcg EE treatment group when that group was terminated due to an unacceptably high rate of endometrial hyperplasia.

Inclusion criteria included the following:

- asymptomatic or mildly symptomatic women of any race,
- age $\geq$ 40 years,
- $\leq$ 5 years postmenopausal,
- diagnosis of atrophy on endometrial biopsy,
- FSH $\geq$ 40 miu/ml and estradiol $\leq$ 20 pg/ml,
- No prior use of estrogens or progestins or calcitonin for at least 6 months prior to study enrollment,
- Within 20% of ideal body weight, according to the 1979 Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America, 1980,
- normal trabecular lumbar spine BMD $\geq$ 90 - 160 mg/cm by quantitative computerized tomography .

Reviewer's Comments: The sponsor did not have a young (30 year old) or an age-matched, sex-matched reference population for calculation of T-scores and Z-scores, respectively. In the literature, lumbar spine BMD for non-osteoporotic women is reported to be in the 90-160 mg/cc range for women aged 48-52. (Cann CE, Genant HK, Kolb FO, Ettinger B Quantitative Computed Tomography for Prediction of Vertebral Fracture Risk, Bone 6: 1-7, 1985) (Kalendar WA, Felsenberg D, Louis O, Lopez P, Klotz E, Osteaux M, Fraga J. Reference Values for Trabecular and Cortical Vertebral Bone Density in Single and Dual-Energy Computed

Tomography, Europ J Radiol 9: 75-80, 1989.) The sponsor was also unable to clarify if the QCT methodology used in this study was single energy or dual energy. Single energy QCT incorporates measurement of fat, while dual energy QCT corrects for it.

Exclusion criteria included the following:

- Current or past history of breast cancer, ovarian cancer, endometrial cancer;
- Current or past history of thromboembolic, cardiovascular, or coronary artery disease;
- History of alcoholism in past 3 years;
- Current vaginal bleeding;
- Mammogram results suspicious of malignant disease;
- Significant vasomotor symptoms requiring therapy;
- Diseases affecting bone metabolism, such as hyper- or hypocalcemia, hyperthyroidism, osteogenesis imperfecta, malignancy, chronic granulomatous disease, Paget's disease;
- Chronic use of medications affecting bone calcium metabolism, such as systemic corticosteroids, anticonvulsants, calcium, aluminum, or magnesium-containing anatacids; thiazide diuretics; fluoride in excess 1 mg/day; supplemental vitamin A or D.
- Systolic BP >150 mm Hg; Diastolic BP > 90 mm Hg. Patients with controlled hypertension could be included.
- Diabetes Mellitus, defined as fasting glucose > 110 mg/dl or random glucose > 140 mg/dl.
- Liver disease, defined as SGOT and/or SGPT > 2x upper limit of normal.
- Renal disease, defined as BUN > 30 mg/dl or serum creatinine > 2 mg/dl.
- Hypercholesterolemia, defined as LDL cholesterol > 190 mg/dl.
- Use of lipid-lowering drugs (cholestyramine, clofibrate, colestipol, dextrothyroxine, gemfibrozil, lovastatin, niacin, omega three fatty acids, probucol.)
- Current or prior gall bladder disease; patients with prior cholecystectomy could be included.
- Participation in any clinical trial within prior 4 weeks.
- Any patient in whom investigator believes estrogen and/or a progestin are contraindicated.
- Any patient incapable of understanding the necessary instructions or not reasonably expected to complete the 24 month study.

The schedule of clinic visits, observations, and procedures is outlined below (note month -1 refers to 30 day screening period before randomization):

- Clinic visits – months –1, 1, 3, 6, 9, 12, 18, and 24;
- Medical history – month –1;
- Physical exam – months –1, 12, 24;
- Pelvic exam/endometrial biopsy – months –1, 6, 12, 18, 24.
- Mammography – months –1, 12, 24.
- Quantitative Computerized Tomography (QCT) scan of lumbar vertebrae – months –1, 12, 24;
- Clinical Laboratory Urine and Blood Chemistry – months –1, 12, 24;
- Serum FSH and estradiol – months –1;
- Medication dispensation – months –1, 1, 3, 6, 9, 12, 18;
- Clinical evaluation (including weight, BP, HR; review of bleeding/spotting) – months 1, 3, 6, 9, 12, 18, 24. Note: Heights were measured at baseline but no height measurements at completion of study are included in the NDA.

Quantitative Computed Tomography (QCT) Methodology

The bone mineral density quality assurance program was recommended by [redacted] of the [redacted] and included quantitative computed tomography (QCT) technologist training, machine cross-calibration, and machine longitudinal calibration. Training for technologists included a 9/22/90 meeting, sessions covering both clinical and technical issues of bone densitometry, and availability of the [redacted] for questions. Two standardization procedures were available for CT scanners that used calibration phantoms containing different concentrations of bone equivalent material: (1) a simultaneous scanning of the calibration phantom with the patient or (2) a scanning of the phantom before or after the patient scan. Guidelines for Quality Assurance Measurements also assisted the technologists in maintaining consistent technique throughout the study. In addition, each CT system was characterized using an [redacted] phantom, manufactured by the [redacted] A series of each torso phantom with different inserts simulating different body and bone compositions were obtained for calibration of the following: patient size, marrow fat content, linearity of true versus measured BMD, calibration procedure, and CT scanners. These scans also provided information about patient position within the scan field and scanner characterizations were evaluated centrally at the [redacted] A torso phantom manufactured by [redacted] was scanned periodically to document long-term drifts and transitional problems.

Investigators recorded the patient's bone mineral density onto Case Report 5 in mg/cc. Form 5 data refer to uncorrected data. Corrected data were those data available for standardization across all study sites and were compared to the standard site [redacted] Bone mineral densities for individual vertebral bodies were entered into Case Report 12 in either mg/cc or Hounsfield units. Densities were recorded for vertebral bodies T11, T12, L1-L5, and S1. For each follow-up CT scan, a baseline and follow-up density average were computed after the study completed by averaging, for each scan, the vertebral bodies in common between the 2 visits. Crush fractured vertebral bodies were excluded from the poststudy averages.

Enrollment and completion of subjects in the osteoporosis studies according to different analyses is outlined in the table below:

APPEARS THIS WAY
ON ORIGINAL

Number (%) of Subjects in Osteoporosis Studies (adapted from Tables 7 [ISS p. 26 of 86], Table 12 [ISE p.38 of 162], App. C 4-6 [pp662-4])																
Study	Placebo	**Fem HRT (mgNA/EEmcg)**							total Fem HRT	**EE (mcg)**				Total EE	MPA /CEE	Total
		0.2/1	**.5/2.5**	**0.5/5**	**1/5**	**.5/10**	**1/10**	**1/20**		**1**	**2.5**	**5**	**10[a]**			
376-343 Randomized	10			12	14	13	14	12	65						12	87
At 12 months	10			11	10	12	13	11							8	
Open-label	5			9	9	11	13								4	
Year 5	5			9	7	9	12								1	
376-359 Randomized	137	139	136		146		145		566	141	137	141	143	562		1265
Intent To Treat (ITT)	123 (90)	119 (86)	120 (88)		124 (85)		118 (81)			119 (84)	119 (88)	121 (86)	101 (71)			1065 (84)
Observed at 12 months	109 (80)	105 (76)	110 (81)		111 (76)		105 (72)			108 (77)	111 (81)	112 (79)	60 (42)			931 (74)
Observed at 24 months	97 (71)	99 (71)	99 (73)		102 (70)		98 (68)			96 (68)	92 (67)	105 (74)	14 (10)			802 (65)
Evaluable at 12 months	98 (72)	94 (68)	93 (68)		96 (66)		92 (63)			92 (65)	96 (70)	99 (70)	51 (36)			811 (64)
Evaluable at 24 months	86 (63)	86 (62)	85 (62)		89 (61)		88 (61)			81 (57)	80 (58)	90 (64)	10 (7)			695 (55)

[a] The 10 mcg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia.

8.2.3.2 Evaluability Criteria and Defined Clinical Endpoints

Primary efficacy parameters included bone mineral density (BMD) as measured by QCT scan and the incidence of endometrial hyperplasia as determined by endometrial biopsy. For BMD, the actual change from baseline was the primary response of interest and the effectiveness of NA/EE in maintaining BMD was evaluated by comparisons of each dose of the combination with placebo. The dose response of NA/EE including placebo was also examined. Effectiveness of NA/EE treatment in prevention of endometrial hyperplasia was evaluated by pairwise comparisons of the proportion of patients with hyperplasia in each NA/EE treatment group with that in the corresponding unopposed EE treatment group.

Secondary efficacy parameters: Vaginal bleeding or spotting and the average monthly duration of bleeding or spotting (in days) at clinic visits were examined. Actual and percent change form baseline in lipid parameters – serum total cholesterol, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides were also evaluated. Reviewer's comment: There were no measurements of appendicular BMD or biochemical bone markers, e.g., serum osteocalcin or urinary pyridinoline or deoxypyridinoline/creatinine ratios, in this study. In addition, there was no formal assessment of vertebral or other fractures. One would not expect many fractures in a population of postmenopausal women with normal BMD for their age.

Safety monitoring included screening medical history, physical examination, Pap smear, endometrial biopsy, mammography and samples for clinical laboratory analysis; monitoring for spontaneously volunteered adverse events at each clinic visit and indirect questioning for possible adverse events. (Reviewer's comment: this indirect approach may elicit less adverse events.) Investigators assessed relationship of adverse events in terms of relationship to drug (definitely, probably, possibly, unlikely, definitely not, or unknown) before study blind was broken.

8.2.3.3 Statistical Considerations

Changes from baseline in bone mineral density (BMD) were analyzed using analysis of variance (ANCOVA) with effects of center, treatment, and baseline BMD as covariates. The primary comparisons of interest were each NA/EE treatment group versus placebo using Dunnett's test on the least-square means, and dose response of the NA/EE treatment groups including placebo, using a linear trend contrast (orthogonal polynomial) based on the rank dose of each estrogen component in the combination to generate contrast coefficients. Secondary comparisons of interest were each NA/EE versus the corresponding unopposed EE treatment group and dose response of the NA/EE treatment groups excluding placebo. Mean change in baseline BMD was also computed stratified by years since menopause, as specified in protocol, and by activity level at baseline (an analysis planned after unblinding of the data) and smoking status at baseline (analysis planned prior to study completion).

Reviewer's comments:

For the bone mineral density change, the protocol describes a comparison of each treatment group versus placebo. As discussed with the statistical team, there is no *a priori* description of a comparison among treatment groups, allowing for multiple comparisons for the bone mineral density data. Thus, from this study it is possible to say whether a treatment group had a greater effect on bone mineral

density than the placebo group, but it is more difficult to conclude *post hoc* whether one treatment group was better than another. When a Bonferroni adjustment was used to assess the statistical significance of treatment differences comparing each NA/EE dose to the corresponding EE dose alone, only one of the comparisons would have been barely significant. The analyses planned after the original protocol are considered in this review for possible support of the osteoporosis indication sought by the sponsor, but are not as primary.

The sponsor has provided three sets of analyses of lumbar spine density based on different post hoc inclusion criteria: intent-to-treat, observed cases, and evaluable. The intent-to-treat analysis is presented in two ways. The sponsor cites the evaluable analysis as primary and supports it with two other analyses. The exclusion criteria and the actual n included in the analyses are listed in the table below :

Type of Analysis	**Criteria for Patient Inclusion**	**N included in analysis** Randomized N = 1265 (% of Randomized)
Intent-to-Treat	• Baseline and a followup BMD • At least 1 dose of study medication taken	• 1065 (84%)
Observed Cases at 12 and 24 months	• Baseline and followup BMD within 12 month and 24 month time windows • At least 1 dose of study medication taken	• 931 (12 months) (74%) • 802 (24 months) (65%)
Evaluable	• No systemic sex hormones or calcitonin taken within 150 days of baseline BMD measurement (Note: this exclusion applied to 4 patients in the EE treatment groups only) • Baseline and evaluable followup BMD • At least 1 dose of study medication taken	• 811 (12 months) (64%) • 695 (24 months) (55%)

Criteria for Evaluable Bone Mineral Density (BMD) Measurements

Bone mineral density (BMD) measurements were excluded from evaluable analysis if they met the following criteria: (See sponsor's Appendix C1 CT Exclusions page 2 of 2) [total n excluded for criterion across treatment groups is listed]

- Measurement made ≥ 60 days after termination of treatment; [n=27]
- Measurement not made within specified time window; [n=0]
- Measurements taken during double-blind use utilized different vertebrae than at baseline;
- Measurement taken used only vertebrae;[n=10]
- Vertebral bodies were measured in Hounsfield units but lacked measurements on the phantom inserts for transformation of BMD from Hounsfield units to mg/cc; [n=36]

- Scan information did not include measurements on individual vertebral bodies so that an average over vertebral bodies could not be computed; [n=122]
- Measurement was made after it was reported that the patient received the wrong medication unless documentation exists that the patient received the correct treatment for ≥ 90 days immediately before the CT scan and was reasonably compliant; [n=2]
- Measurement made after the initiation of concurrent chronic treatment (>30 d) with fluroride, calcitonin, phenytoin, or sex steroids; [n=0]
- Measurements had no cross-calibration data QA procedures performed by [redacted] [n=266]

Reviewer's comments:

- Based on E9 Statistical Principles for Clinical Trials, Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98, the primary preferred FDA analysis is the Intent-To-Treat and in this review that was the primary analysis evaluated.
- Since the exclusions represented 16% (200/1265) of the Intent-to-Treat group, the option of having the sponsor provide confirmatory Intent-to-Treat analyses, imputing 0 change and mean placebo change for missing followup measurements was discussed with the statistical team. These confirmatory analyses were not requested because (1) the percentage of missing data was less than 15%, except for the 10 mcg EE treatment group (29%), which was terminated because of endometrial hyperplasia and (2) the p-values were highly significant ($p<.0001$).
- The number of exclusions for each of the three analyses was equally distributed among all groups, except for the 10 mcg EE treatment group, which was termintated because of the high rate of endometrial hyperplasia. This relatively equal distribution of exclusions among the other treatment groups makes a specific bias in favor of a treatment group because of the exclusions less likely.
- The respective exclusions accounted for exclusion of 26% (334/1265) of the patients in the 12 month observed cases analysis, 37% (463/1265) in the 24 month observed cases analysis, and 36 % (452/1265) in the 12 month evaluable analysis, and 45% (568/1265) in the 24 month evaluable analysis.
- As identified by the sponsor, those patients who were considered non-evaluable because of non-evaluable BMD measurements were relatively evenly distributed among the different treatment groups for the different criteria. (See sponsor's Table 11 "Exclusions from Bone Mineral Density Efficacy Analyses" and Appendix C1 CT Exclusions)

TABLE 11. Exclusions From Bone-Mineral Density Efficacy Analyses
(Number of Patients)

Analysis/Reason for Exclusion	Placebo N = 137	NA/EE Treatment Group, mg/µg 0.2/1 N = 139	0.5/2.5 N = 136	1/5 N = 146	1/10 N = 145	EE Treatment Group, µg 1 N = 141	2.5 N = 137	5 N = 141	10 N = 143	Overall N = 1265
Intent-to-Treat Analysis										
No Baseline or Follow-up BMD	14	20	16	22	27	22	17	20	42	200
No Study Medication Was Taken	0	1	0	0	1	0	2	0	0	4
Any[a]	14	20	16	22	27	22	17	20	42[b]	200
Observed Cases Analysis, Month 12										
No Baseline BMD or No Follow-up BMD Within Month 12 Time Window	28	34	26	35	40	33	26	29	83	334
No Study Medication Was Taken	0	1	0	0	1	0	2	0	0	4
Any[a]	28	34	26	35	40	33	26	29	83	334
Observed Cases Analysis, Month 24										
No Baseline BMD or No Follow-up BMD Within Month 24 Time Window	40	40	37	44	47	45	45	36	129	463
No Study Medication Was Taken	0	1	0	0	1	0	2	0	0	4
Any[a]	40	40	37	44	47	45	45	36	129	463
Evaluable Analysis, All Time Points										
Systemic Sex Hormones or Calcitonin Taken Within 150 Days of the Baseline BMD	0	0	0	0	0	1	2	1	0	4
No Study Medication Was Taken	0	1	0	0	1	0	2	0	0	4
Evaluable Analysis, Month 12										
No Evaluable Baseline BMD or No Evaluable Follow-Up BMD Within the Month 12 Time Window	39	45	43	50	53	49	40	41	92	452
Any[a]	39	45	43	50	53	49	41	42	92	454
Evaluable Analysis, Month 24										
No Evaluable Baseline BMD or No Evaluable Follow-Up BMD Within the Month 24 Time Window	51	53	51	57	57	60	56	50	133	568
Any[a]	51	53	51	57	57	60	57	51	133	570

BMD = Bone-Mineral Density
[a] Patients could have > 1 reason for exclusion.
[b] One additional patient, Patient 3, Center 70, did not have Form 5 data, and was not included in the analysis of uncorrected Form 5 BMD.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX C.1

CT EXCLUSIONS
(Page 2 of 2)

Exclusions of CT* Scans From Evaluable Bone-Mineral Density Analyses
(Number of Scans)

Reason	Placebo N = 137	NA/EE Treatment Group 0.2/1 N = 137	0.5/2.5 N = 139	1/5 N = 146	1/10 N = 145	EE Treatment Group 1 N = 141	2.5 N = 137	5 N = 141	10 N = 143
BMD Measured > 60 Days After Termination of Treatment	2	1	2	6	2	5	3	1	5
Follow-Up Uses Different Vertebral Bodies From Baseline	0	0	0	0	0	0	0	0	0
Measurement Used Only 1 Vertebrae	0	2	0	2	0	0	2	2	2
Vertebral Bodies Measured in Hounsfield Units but no Measurements on Phantom Inserts	4	3	6	5	5	2	5	3	3
No Individual Vertebrae Densities	12	14	16	9	13	13	11	18	16
The BMD Was Measured After Patient Took Wrong Medication	0	1	0	0	1	0	0	0	0
Measurement Made After Initiation of Concurrent Chronic Treatment (>30 Days) With Fluoride, Calcitonin, Phenytoin, or Sex Steroids	0	0	0	0	0	0	0	0	0
No Cross-Calibration Data From	30	27	27	32	29	31	30	33	27

* Computed tomography

8.2.3.4 Study Results

8.2.3.4.1 Demographics, Evaluability

Patient characteristics were provided for all randomized patients (See Table "Baseline Patient Characteristics", which was provided by the sponsor upon FDA request). Patient characteristics were comparable across treatment groups, as indicated by the non-significant p-values, which were not included in the NDA. The average age was 52 (± 4) with 95% White. The mean number of months since the last menstrual period was 31. The overall percentage of women who

Protocol 376-359
Baseline Patient Characteristics
All Randomized Patients

	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg				
	Placebo	**0.2/1**	**0.5/2.5**	**1/5**	**1/10**	**1**	**2.5**	**5**	**10**	**p-value**
N	137	139	136	146	145	141	137	141	143	
Age										0.9627 [a]
Mean (SD)	51.7 (4.1)	52.5 (3.9)	51.8 (4.2)	51.6 (4.0)	52.1 (3.6)	52.2 (4.1)	51.8 (4.2)	52.0 (4.0)	51.9 (4.4)	
Median (min, max)	52 (41, 62)	52 (40, 64)	53 (40, 60)	52 (42, 63)	52 (40, 62)	53 (40, 63)	52 (40, 62)	52 (40, 63)	52 (40, 62)	
Months Since Last Menstrual Period										0.1740 [a]
Mean (SD)	31.5 (20.2)	33.1 (16.0)	32.3 (16.5)	31.2 (17.3)	30.7 (18.9)	31.8 (16.5)	29.2 (19.5)	32.8 (19.4)	29.1 (17.2)	
Median (min, max)	31.0 (2, 154)	32.0 (4, 61)	31.0 (6, 68)	30.5 (1, 79)	29.0 (4, 116)	33.0 (1, 60)	24.5 (2, 122)	32.0 (1, 108)	27.0 (4, 67)	
Race, n (%)										0.771 [b]
White	131 (96)	129 (93)	128 (94)	135 (93)	141 (97)	134 (95)	132 (96)	135 (96)	137 (96)	
Black	2 (2)	1 (1)	3 (2)	2 (1)	0 (0)	3 (2)	1 (1)	2 (1)	2 (1)	
Other	4 (3)	9 (7)	5 (4)	9 (6)	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	
Physically Active, n (%)										0.585 [b]
Yes	87 (64)	92 (66)	85 (62)	98 (67)	86 (59)	86 (61)	79 (58)	84 (60)	97 (68)	
No	50 (36)	47 (34)	51 (38)	48 (33)	59 (41)	55 (39)	58 (42)	57 (40)	46 (32)	
Smoking History, n (%)										0.554 [b]
Never	62 (45)	68 (49)	59 (43)	72 (49)	61 (42)	64 (45)	59 (43)	64 (45)	59 (41)	
Stopped	41 (30)	35 (25)	43 (32)	36 (25)	48 (33)	54 (38)	45 (33)	45 (32)	43 (30)	
Light	9 (7)	14 (10)	8 (6)	12 (8)	7 (5)	8 (6)	11 (8)	10 (7)	14 (10)	
Moderate	22 (16)	17 (12)	16 (12)	21 (14)	18 (12)	10 (7)	18 (13)	13 (9)	21 (15)	
Heavy	3 (2)	5 (4)	10 (7)	5 (3)	11 (8)	5 (4)	4 (3)	9 (6)	6 (4)	

[a] From Analysis of Variance
[b] From Chi-Square test

Protocol 376-359
Baseline Patient Characteristics
All Randomized Patients (Cont.)

	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg				
	Placebo	0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10	p-value
N	137	139	136	146	145	141	137	141	143	
Systolic Blood Pressure, mm Hg										0.3649 [a]
Mean (SD)	119 (12.8)	122 (15.1)	120 (16.5)	118 (13.4)	122 (14.9)	120 (14.8)	119 (13.2)	119 (14.2)	119 (12.6)	
Diastolic Blood Pressure, mm Hg										0.9892 [a]
Mean (SD)	75 (8.6)	77 (8.2)	75 (8.7)	75 (8.6)	76 (7.9)	76 (8.7)	76 (8.4)	76 (8.6)	75 (8.8)	
Weight, kg										0.1404 [a]
Mean (SD)	63 (9.2)	65 (9.3)	66 (9.4)	64 (8.9)	65 (9.7)	66 (8.8)	65 (9.2)	65 (9.5)	66 (9.1)	
Height, cm										0.5336 [a]
Mean (SD)	163 (7.1)	165 (5.7)	164 (6.0)	163 (7.1)	164 (6.4)	165 (5.8)	164 (6.7)	164 (6.7)	163 (10.5)	

[a] From Analysis of Variance

[b] From Chi-Square test

APPEARS THIS WAY
ON ORIGINAL

never smoked was 45%; 31% were former smokers; 7% light smokers; 12% moderate smokers; and 5% heavy smokers. The mean blood pressure was 120 (± 14.2) /76(±8.5), the mean weight was 65 (±9.2) kg and the mean height was 164.0 (± 7.1)cm. The mean body mass index was approximately 24 kg/m^2, which is indicative of the fairly lean patient population recruited for this study (weight < 20% above ideal body weight) and did not vary among the treatment groups.

Estrogen and progestin use for the six months prior to study enrollment was an exclusion criterion. However, approximately 30% of the subjects had previously used hormone replacement therapy and approximately 60% of the subjects used oral contraceptives. The prior use of these hormones was equally represented among the different treatment groups, as noted in the sponsor's Table 6 Summary of Prior Estrogens / Progestins.

TABLE 10. Patient Disposition
[Number (%) of Patients]

	Placebo	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg				Overall
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10	
Randomized to Treatment	137	139	136	146	145	141	137	141	143	1265
Withdrawals										
Adverse Events	14 (10)	14 (10)	11 (8)	25 (17)	24 (17)	18 (13)	16 (12)	19 (13)	30 (21)	171 (14)
Sponsor Request[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	96 (67)	96 (8)
Personal Reasons	6 (4)	12 (9)	11 (8)	7 (5)	10 (7)	10 (7)	13 (9)	7 (5)	5 (3)	81 (6)
Lost to Follow-up	4 (3)	6 (4)	6 (4)	6 (4)	5 (3)	6 (4)	5 (4)	3 (2)	4 (3)	45 (4)
Lack of Compliance	2 (1)	3 (2)	4 (3)	2 (1)	3 (2)	6 (4)	5 (4)	8 (6)	2 (1)	35 (3)
Lack of Efficacy	3 (2)	0 (0)	1 (1)	0 (0)	0 (0)	2 (1)	1 (1)	0 (0)	0 (0)	7 (1)
Death	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)
Administrative Reasons	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	2 (0)
Unable to Biopsy	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	2 (0)
Total Withdrawn	30 (22)	38 (27)	33 (24)	41 (28)	42 (29)	42 (30)	41 (30)	37 (26)	139 (97)	443 (35)
Months of Treatment Completed[b]										
Month 6	127 (93)	127 (91)	120 (88)	128 (88)	116 (80)	124 (88)	122 (89)	129 (91)	98 (69)	1091 (86)
Month 12	119 (87)	114 (82)	110 (81)	117 (80)	111 (77)	109 (77)	112 (82)	115 (82)	47 (33)	954 (75)
Month 18	110 (80)	109 (78)	105 (77)	113 (77)	107 (74)	101 (72)	101 (74)	111 (79)	14 (10)	871 (69)
Month 24	93 (68)	86 (62)	92 (68)	93 (64)	93 (64)	86 (61)	84 (61)	92 (65)	3 (2)	722 (57)
Completed Study	108 (79)	102 (73)	103 (76)	105 (72)	103 (71)	99 (70)	96 (70)	104 (74)	4 (3)	824 (65)

[a] The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.
[b] Patient's last day on drug ≥ number of months x 30 days/month

RR 720-03121

35

Please refer to above general discussion under Statistical Considerations regarding evaluability and to Table Number of Subjects in Osteoporosis Studies regarding the number of patients evaluable for the different analyses presented by the sponsor. 1065 or 84% of the randomized subjects were available for the Intent-To-Treat analysis of BMD. These subjects had at least one followup BMD measurement. 811 or 64% of the randomized subjects completed the 24 month observations and 695 or 55% of the randomized subjects had evaluable data at 24 months. Considering that this study was fairly demanding, requiring endometrial biopsies every 6 months and a bone mineral density assessment by quantitative computed tomography annually, it is impressive that so many subjects participated in most of the study. Withdrawals from study are shown in the sponsor's Table 10 Patient Disposition. More

subjects withdrew for adverse events in the 1/5 and 1/10 mg NA/mcgEE treatment groups than in placebo or the lower dosages. "Completed Study" was an investigator descriptor and thus more patients are listed in this category than under 24 month completion.

8.2.3.4.2 Clinical Efficacy

Change in Bone Mineral Density (BMD)

The sponsor's intent-to-treat, observed cases, and evaluable analyses adjusted for baseline BMD, center, and treatment all indicate a statistical improvement in lumbar spine bone mineral density as compared to baseline and to placebo for the NA/EE 1/5 and 1/10 treatment groups (p=0.0001). (See sponsor's Tables 17, 18, Appendix C-4, C-6, C-5, Tables 14, 15.) The numbers discussed in this section refer to Intent-To-Treat data for last observation carried forward based on corrected data as outlined in the sponsor's Appendix C4. The bone mineral density in the placebo (only calcium-treated) group decreases by 7.7 $\pm$ 1.2 gm/cc from a baseline of 119.5 mg/cc, which represents a 6.3 $\pm$ 1.1 negative percent change from baseline. The treatment groups 0.2/1 mgNA/mcgEE was not different from baseline or placebo. The treatment group 0.5/2.5 mgNA/mcgEE showed slight improvement in comparison to placebo, but was not statistically significant from baseline. Thus this treatment group maintained bone density. In the 1/5 mgNA/mcgEE treatment group, there is a 3.1 $\pm$ 1.2 mg/cc increment above the baseline 117.8 $\pm$ 1.56 mg/cc bone mineral density which translates to a 3.1 $\pm$ 1.1% percent change from baseline. Thus, the treatment effect (percent change in a NA/EE treatment group minus percent change in placebo) in percent change is 9.4% for 1/5 mgNA/mcgEE and 10.8% for the 1/10 mgNA/mcgEE.

In addition, the dose response trend of the NA/EE treatment group was statistically significant both including and not including placebo for all of the three analyses, the Intent-to-Treat, the observed cases, and the evaluable analyses, confirming an increasing linear dose response trend (p=0.0001). A t-test statistic comparing the change in lumbar spine BMD between the 1/5 and 1/10 mgNA/mcgEE treatment doses was performed by the FDA statistician and was found not to be significant.

Reviewer's Comments:

(1) The large decrement in BMD in the placebo group may reflect the low calcium supplementation (1000 mg daily) and absence of vitamin D supplementation
(2) The 0.2/1 mg NA/mcgEE was the nonefficacious dosage, revealing no change in BMD from placebo and from baseline.
(3) The 0.5/2.5 mgNA/mcgEE dosage was efficacious in maintaining bone mineral density, revealing no change from baseline but a significant change from placebo.
(4) The 1/5 and 1/10 mgNA/mcgEE were both efficacious in the prevention of BMD loss. Despite a significant dose response trend for the NA/EE treatment groups (with or without placebo), there is no statistical difference in the comparison of the BMD change results between the 1/5 and 1/10 treatment groups.

(5) Because of the large decrement in BMD in the placebo group, the treatment effect (BMD change in NA/EE treatment group minus change in placebo) may appear disproportionally large.

APPEARS THIS WAY
ON ORIGINAL

TABLE 17. Summary of Mean (SE) Uncorrected Form 5 Bone-Mineral Density
Intent-to-Treat Population

Time	Placebo	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Month 24									
N	123	119	120	124	118	119	120	121	100
Baseline, mg/cc	124.8 (1.99)	123.4 (1.64)	125.4 (1.89)	123.3 (1.57)	124.9 (1.80)	125.0 (1.69)	121.6 (1.91)	123.1 (1.79)	125.7 (1.94)
Follow-Up, mg/cc	117.9 (2.22)	121.9 (1.85)	123.4 (1.90)	128.0 (1.98)	131.5 (2.33)	121.4 (2.03)	120.1 (2.08)	120.9 (2.09)	129.4 (2.17)
Change From Baseline, mg/cc	-6.9 (1.39)	-1.5 (1.23)	-2.0 (1.37)	4.8 (1.29)	6.5 (1.51)	-3.6 (1.40)	-1.6 (1.21)	-2.2 (1.54)	3.6 (1.05)
Percent Change	-5.4 (1.09)	-0.9 (0.99)	-0.8 (1.10)	4.0 (1.07)	5.4 (1.19)	-2.6 (1.11)	-1.0 (0.97)	-1.4 (1.29)	3.0 (0.84)

SE = Standard error.
[a] The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

TABLE 18. Adjusted (Least-Squares Estimate) Mean (SE) Change From Baseline in Uncorrected Form 5 Bone-Mineral Density

Intent-to-Treat Population

Time	Placebo	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Month 24									
N	123	119	120	124	118	119	120	121	100
Change From Baseline, mg/cc	-4.8 (1.18)	-0.2 (1.21)	-0.5 (1.20)	6.3 (1.18)	8.2 (1.20)	-2.3 (1.21)	-0.6 (1.20)	-0.6 (1.20)	5.6 (1.31)
p-Value[b] (NA/EE or EE vs Placebo)	--	0.0094	0.0162	0.0001	0.0001	0.1786	0.0183	0.0175	0.0001
95% Confidence Interval[c] (NA/EE or EE vs Placebo), mg/cc	--	[1.0, ∞]	[0.7, ∞]	[7.6, ∞]	[9.4, ∞]	[-1.0, ∞]	[0.7, ∞]	[0.7, ∞]	[6.7, ∞]
p-Value[d] (Follow-up vs Baseline)	0.0001	0.8749	0.6656	0.0001	0.0001	0.0604	0.6274	0.6416	0.0001
p-Value[e] (NA/EE vs EE)	--	0.2087	0.9706	0.0001	0.1437	--	--	--	--

SE = Standard error.
[a] The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.
[b] The null hypothesis is that the mean change in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.
[c] For difference in mean changes between the NA/EE or EE treatment group and placebo group; 1-sided confidence interval.
[d] The null hypothesis is that the mean change from baseline is equal to zero.
[e] The null hypothesis is that the mean changes in the NA/EE and corresponding EE treatment groups are equal.

APPENDIX C.4

SUMMARY OF MEAN (SE) AND ADJUSTED (LEAST-SQUARES ESTIMATE)
MEAN (SE) CHANGE IN BONE-MINERAL DENSITY (MG/CC) BASED ON CORRECTED DATA IF AVAILABLE
INTENT-TO-TREAT POPULATION

Time	Placebo	NA/EE Treatment Group				EE Treatment Group			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Mean Bone-Mineral Density									
Month 24									
N	123	119	120	124	118	119	120	121	101
Baseline	119.5 (2.03)	120.2 (1.79)	119.8 (1.85)	117.8 (1.56)	119.4 (1.86)	119.8 (1.73)	116.9 (1.63)	119.1 (1.79)	120.2 (1.96)
Follow-Up	111.8 (2.14)	116.9 (1.71)	117.4 (1.80)	121.0 (1.86)	124.2 (2.06)	116.9 (1.96)	114.4 (1.87)	117.2 (2.08)	123.0 (2.08)
Change From Baseline	-7.7 (1.24)	-3.3 (1.45)	-2.4 (1.37)	3.1 (1.24)	4.8 (1.32)	-2.9 (1.43)	-2.5 (1.07)	-1.8 (1.57)	2.8 (0.90)
Percent Change	-6.3 (1.10)	-2.1 (1.03)	-0.8 (1.49)	3.1 (1.11)	4.5 (1.13)	-2.0 (1.27)	-2.0 (0.92)	-0.9 (1.56)	2.5 (0.79)
Adjusted Mean Bone-Mineral Density									
Month 24									
N	123	119	120	124	118	119	120	121	101
Change From Baseline	-5.7 (1.16)	-1.8 (1.19)	-0.8 (1.18)	4.6 (1.16)	6.5 (1.18)	-1.6 (1.19)	-1.2 (1.18)	-0.2 (1.18)	4.4 (1.28)
p-Value[b] (NA/EE or EE vs Placebo)	--	0.0308	0.0046	0.0001	0.0001	0.0207	0.0098	0.0012	0.0001
p-Value[c] (Follow-up vs Baseline)	0.0001	0.1206	0.5079	0.0001	0.0001	0.1817	0.3205	0.8958	0.0007
95% Confidence Interval[d] (NA/EE or EE vs Placebo)	--	[0.3, ∞]	[1.4, ∞]	[6.8, ∞]	[8.6, ∞]	[0.6, ∞]	[1.0, ∞]	[2.0, ∞]	[6.4, ∞]
p-Value[e] (NA/EE vs EE)	--	0.0740	0.8123	0.0034	0.2185	--	--	--	--

SE = Standard error.
[a] The 10 μg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.
[b] The null hypothesis is that the mean changes in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.
[c] The null hypothesis is that the mean change from baseline is equal to zero.
[d] For difference in mean changes between the NA/EE or EE treatment group and placebo group; 1-sided confidence interval.
[e] The null hypothesis is that the mean changes in the NA/EE and corresponding EE treatment groups are equal.

APPENDIX C.6

ADJUSTED (LEAST-SQUARES ESTIMATE) MEAN (SE) CHANGE FROM BASELINE IN BONE-MINERAL DENSITY (MG/CC) OBSERVED CASES DATA

Time	Placebo	NA/EE Treatment Group				EE Treatment Group			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Corrected Bone-Mineral Density									
Month 12									
N	109	105	110	111	105	108	111	112	60
Change From Baseline	-2.9 (1.04)	-1.4 (1.07)	0.5 (1.04)	5.4 (1.03)	5.7 (1.05)	-0.3 (1.04)	-0.5 (1.02)	0.2 (1.03)	3.7 (1.38)
p-Value[b] (NA/EE or EE vs Placebo)	–	0.3456	0.0301	0.0001	0.0001	0.1090	0.1304	0.0506	0.0002
p-Value[c] (Follow-up vs Baseline)	0.0058	0.2020	0.6623	0.0001	0.0001	0.7487	0.6385	0.8829	0.0081
95% Confidence Interval[d] (NA/EE or EE vs Placebo)	–	[-1.6, ∞]	[0.3, ∞]	[3.3, ∞]	[3.5, ∞]	[-0.5, ∞]	[-0.6, ∞]	[-0.0, ∞]	[2.9, ∞]
p-Value[e] (NA/EE vs EE)	–	0.4696	0.5045	0.0001	0.2334	–	–	–	–
Month 24									
N	97	99	99	102	98	96	92	105	14
Change From Baseline	-5.1 (1.37)	-1.7 (1.35)	-0.5 (1.35)	5.9 (1.34)	7.2 (1.34)	-1.5 (1.36)	-0.5 (1.41)	0.3 (1.32)	1.9 (3.52)
p-Value[b] (NA/EE or EE vs Placebo)	–	0.1001	0.0229	0.0001	0.0001	0.0872	0.0261	0.0054	0.1043
p-Value[c] (Follow-up vs Baseline)	0.0002	0.2092	0.6950	0.0001	0.0001	0.2804	0.7254	0.7997	0.5830
95% Confidence Interval[d] (NA/EE or EE vs Placebo)	–	[-0.6, ∞]	[0.6, ∞]	[7.0, ∞]	[8.3, ∞]	[-0.5, ∞]	[0.5, ∞]	[1.4, ∞]	[-1.3, ∞]
p-Value[e] (NA/EE vs EE)	–	0.8983	0.9850	0.0017	0.1606	–	–	–	–

SE = Standard error.
[a] The 10 µg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia.
[b] The null hypothesis is that the mean change in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.
[c] The null hypothesis is that the mean change from baseline is equal to zero.
[d] For difference in mean changes between the NA/EE or EE treatment group and placebo group; 1-sided confidence interval.
[e] The null hypothesis is that the mean changes in the NA/EE and corresponding EE treatment groups are equal.

APPENDIX C.5

SUMMARY OF MEAN (SE) BONE-MINERAL DENSITY (MG/CC) OBSERVED CASES DATA

Time	Placebo	NA/EE Treatment Group				EE Treatment Group			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Corrected Bone-Mineral Density									
Month 12									
N	109	105	110	111	105	108	111	112	60
Baseline	119.6 (2.23)	119.6 (1.73)	119.6 (1.96)	118.7 (1.61)	119.8 (2.03)	118.9 (1.84)	117.0 (1.70)	118.3 (1.85)	119.2 (2.68)
Follow-Up	115.6 (2.31)	117.7 (1.93)	119.4 (1.93)	123.3 (1.81)	124.9 (2.11)	118.0 (2.08)	116.1 (1.79)	117.8 (2.01)	122.4 (2.87)
Change From Baseline	-3.9 (0.91)	-1.9 (1.09)	-0.1 (1.40)	4.6 (0.91)	5.2 (1.13)	-0.9 (1.09)	-0.9 (0.87)	-0.5 (1.09)	3.2 (1.32)
Percent Change	-3.5 (0.84)	-1.5 (0.92)	0.9 (1.24)	3.9 (0.83)	4.8 (1.00)	-0.8 (0.94)	-0.6 (0.75)	-0.2 (0.89)	3.0 (1.20)
Month 24									
N	97	99	99	102	98	96	92	105	14
Baseline	120.4 (2.47)	120.2 (2.01)	118.3 (2.05)	118.7 (1.72)	117.9 (2.06)	119.3 (1.97)	116.5 (1.79)	118.7 (1.95)	115.4 (6.02)
Follow-Up	112.5 (2.53)	116.1 (1.92)	116.1 (1.94)	121.2 (2.02)	122.9 (2.30)	116.1 (2.19)	113.3 (2.14)	117.3 (2.26)	116.9 (6.76)
Change From Baseline	-7.9 (1.43)	-4.1 (1.66)	-2.2 (1.54)	2.5 (1.41)	4.9 (1.40)	-3.2 (1.72)	-2.9 (1.28)	-1.3 (1.71)	3.5 (3.20)
Percent Change	-6.4 (1.27)	-2.8 (1.15)	-0.5 (1.74)	2.6 (1.27)	4.6 (1.24)	-2.9 (1.54)	-2.4 (1.09)	-0.5 (1.73)	3.2 (2.82)

SE = Standard error.
[a] The 10 µg EE treatment group was terminated early due to an unacceptably high rate of endometrial hyperplasia.

TABLE 14. Summary of Mean (SE) Bone-Mineral Density Evaluable Data

Time	Placebo	NA/EE Treatment Group, mg/µg				EE Treatment Group, µg			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Month 12									
N	98	94	93	96	92	92	96	99	51
Baseline, mg/cc	120.5 (2.56)	120.1 (1.94)	119.1 (2.29)	117.8 (1.78)	118.8 (2.23)	117.7 (2.02)	117.8 (1.72)	117.8 (2.01)	120.1 (2.99)
Follow-up, mg/cc	115.9 (2.54)	117.7 (2.02)	118.7 (2.14)	122.1 (1.96)	123.2 (2.24)	115.7 (2.22)	115.9 (1.85)	117.0 (2.11)	123.6 (3.30)
Change From Baseline, mg/cc	-4.6 (0.94)	-2.4 (1.15)	-0.4 (1.37)	4.2 (0.89)	4.4 (1.13)	-2.0 (1.17)	-1.2 (0.93)	-0.8 (0.97)	3.5 (1.36)
Percent Change	-4.1 (0.85)	-1.9 (0.98)	0.8 (1.41)	3.5 (0.83)	4.3 (1.02)	-1.7 (1.02)	-0.9 (0.80)	-0.5 (0.84)	3.1 (1.21)
Month 24									
N	86	86	85	89	88	81	80	90	10
Baseline, mg/cc	121.6 (2.63)	120.0 (1.96)	117.3 (2.24)	118.2 (1.87)	117.2 (2.24)	118.2 (2.19)	116.4 (1.81)	117.5 (2.12)	112.9 (6.23)
Follow-up, mg/cc	112.5 (2.71)	115.4 (2.01)	115.3 (2.03)	120.2 (2.16)	121.5 (2.39)	114.8 (2.35)	113.3 (2.31)	115.1 (2.30)	115.5 (8.41)
Change From Baseline, mg/cc	-9.1 (1.34)	-4.6 (1.23)	-2.1 (1.68)	2.0 (1.49)	4.3 (1.41)	-3.4 (1.85)	-3.1 (1.43)	-2.4 (1.66)	2.6 (3.81)
Percent Change	-7.4 (1.37)	-3.6 (0.99)	-0.2 (1.95)	2.2 (1.36)	4.2 (1.27)	-2.1 (1.68)	-2.7 (1.20)	-1.3 (1.82)	2.7 (3.49)

SE = Standard error.
[a] The 10 µg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.

TABLE 15. Adjusted (Least-Squares Estimate) Mean (SE) Change From Baseline in Bone-Mineral Density Evaluable Data

Time	Placebo	NA/EE Treatment Group, mg/µg				EE Treatment Group, µg			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10[a]
Month 12									
N	98	94	93	96	92	92	96	99	51
Change From Baseline, mg/cc	-3.4 (1.09)	-2.0 (1.11)	0.1 (1.12)	4.8 (1.11)	5.0 (1.12)	-1.4 (1.12)	-0.7 (1.10)	-0.5 (1.09)	3.6 (1.49)
p-Value[b] (NA/EE or EE vs Placebo)	--	0.4182	0.0322	0.0001	0.0001	0.2617	0.1066	0.0754	0.0002
95% Confidence Interval[c] (NA/EE or EE vs Placebo), mg/cc	--	(-1.9, ∞)	(0.3, ∞)	(5.0, ∞)	(5.2, ∞)	(-1.3, ∞)	(-0.5, ∞)	(-0.3, ∞)	(3.2, ∞)
p-Value[d] (Follow-up vs Baseline)	0.0021	0.0691	0.9293	0.0001	0.0001	0.1990	0.5249	0.6704	0.0151
p-Value[e] (NA/EE vs EE)	--	0.7006	0.5912	0.0003	0.4498	--	--	--	--
Month 24									
N	86	86	85	89	88	81	80	90	10
Change From Baseline, mg/cc	-6.4 (1.38)	-3.0 (1.36)	-1.1 (1.38)	4.6 (1.35)	6.1 (1.34)	-1.8 (1.39)	-1.5 (1.42)	-1.2 (1.33)	2.5 (3.93)
p-Value[b] (NA/EE or EE vs Placebo)	--	0.0947	0.0076	0.0001	0.0001	0.0267	0.0161	0.0083	0.0567
95% Confidence Interval[c] (NA/EE or EE vs Placebo), mg/cc	--	(-0.5, ∞)	(1.3, ∞)	(7.0, ∞)	(8.6, ∞)	(0.5, ∞)	(0.8, ∞)	(1.2, ∞)	(-0.2, ∞)
p-Value[d] (Follow-up vs Baseline)	0.0001	0.0289	0.4139	0.0007	0.0001	0.1870	0.2971	0.3639	0.5320
p-Value[e] (NA/EE vs EE)	--	0.5430	0.8484	0.0013	0.3731	--	--	--	--

SE = Standard error.
[a] The 10 µg EE treatment group was terminated early (per protocol) due to an unacceptably high rate of endometrial hyperplasia.
[b] The null hypothesis is that the mean change in the NA/EE or EE treatment group is ≤ to the mean change in the placebo group.
[c] For difference in mean changes between the NA/EE or EE treatment group and placebo group; 1-sided confidence interval.
[d] The null hypothesis is that the mean change from baseline is equal to zero.
[e] The null hypothesis is that the mean changes in the NA/EE and corresponding EE treatment groups are equal.

Comparison of NA/EE Treatment Groups

The 1/5 mgNA/mcgEE treatment group and the 5 mcg EE treatment group were the only NA/EE and EE pair that were nominally statistically different, with adjusted changes from baseline of 4.6 ± 1.2 and –0.2 ± 1.2 mg/cc, respectively, (p=0.0034). However, this comparison did not account for the 16 possible pair-wise comparisons between the NA/EE and EE dose groups.

Reviewer's Comments

Using a statistically conservative Bonferroni correction for multiple comparisons, where a Type 1 error of .05 is divided by the number of possible multiple comparisons, statistical significance of this comparison is very doubtful. In addition, one would expect the 1/5 mgNA/mcgEE treatment group to exceed the 5 mcg EE treatment group as 1 mg is metabolically converted to 2.8 mcg EE, so that in some ways the comparison becomes really 7.8 and 5 mcg EE. The lack of statistical significance between the 1/10 mgNA/mcgEE and 10 mcg EE treatment group may reflect partially the discontinuation of a large proportion of the 10 mcg EE group because of endometrial hyperplasia. There was no NA only treatment group to compare the effect of NA alone versus placebo. However, the comparison of the 1/5 mgNA/mcgEE and the 5 mcg EE treatment groups provides a modest reassurance that the addition of the progestagen NA to EE may not be detrimental to the preservation of bone mineral density.

Percent Change in BMD

The sponsor's primary analysis was an analysis of variance, adjusting for baseline BMD, treatment, and center, with change in BMD measured by QCT as the primary efficacy variable. The physician labels for most drug products present percent change in BMD as the primary outcome. In addition, most clinicians use methods for bone densitometry assessment (e.g. [redacted] other than QCT and may not be familiar with the QCT reference measures. Thus, the the sponsor was also asked to assess the statistical significance of percent change in BMD, by the same protocol-described analysis of variance, so that this efficacy measure could be depicted in the physician label. The results are similar in statistical significance for the three analyses – Intent-to-Treat, observed cases, and evaluable, as indicated in the tables below. The magnitude of significance is similar to that observed for the BMD change analyses.

APPEARS THIS WAY
ON ORIGINAL

Protocol 376-359
Percent Change from Baseline in Bone Mineral Density
ITT Data: Corrected & Uncorrected
Reference: Appendix C.4

Month 24	Placebo	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10
N	123	119	120	124	118	119	120	121	101
p-value[a] (NA/EE or EE vs. Placebo)	--	0.0198	0.0008	0.0001	0.0001	0.0150	0.0202	0.0010	0.0001
95% Confidence Interval[b] (NA/EE or EE vs. Placebo)	--	[0.5, ∞]	[2.0, ∞]	[5.7, ∞]	[7.4, ∞]	[0.7, ∞]	[0.5, ∞]	[2.0, ∞]	[5.2, ∞]
p-value[c] (Follow-up vs. Baseline)	0.0001	0.4647	0.5355	0.0001	0.0001	0.5585	0.4545	0.5827	0.0007
p-value[d] (NA/EE vs EE)	--	0.9150	0.3209	0.0109	0.2041	--	--	--	--

[a] The null hypothesis is that the mean change in the NA/EE or EE treatment group is <= to the mean change in the placebo group.
[b] For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.
[c] The null hypothesis is that the mean change from baseline is equal to zero.
[d] The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

Protocol 376-359
Percent Change from Baseline in Bone Mineral Density
ITT Data: Uncorrected Form 5 Data
Reference: Table 17

Month 24	Placebo	NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
		0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10
N	123	119	120	124	118	119	120	121	100
p-value[a] (NA/EE or EE vs. Placebo)	--	0.0071	0.0039	0.0001	0.0001	0.1550	0.0166	0.0100	0.0001
95% Confidence Interval[b] (NA/EE or EE vs. Placebo)	--	[1.0, ∞]	[1.2, ∞]	[6.1, ∞]	[7.4, ∞]	[-0.7, ∞]	[0.6, ∞]	[0.8, ∞]	[5.2, ∞]
p-value[c] (Follow-up vs. Baseline)	0.0001	0.8700	0.6762	0.0001	0.0001	0.1170	0.8140	0.9986	0.0001
p-value[d] (NA/EE vs EE)	--	0.2060	0.6352	0.0001	0.1349	--	--	--	--

[a] The null hypothesis is that the mean change in the NA/EE or EE treatment group is <= to the mean change in the placebo group.
[b] For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.
[c] The null hypothesis is that the mean change from baseline is equal to zero.
[d] The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

Protocol 376-359
Percent Change from Baseline in Bone Mineral Density
Observed Cases Data
Reference: Appendix C.5

		NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
	Placebo	0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10
Month 12									
N	109	105	110	111	105	108	111	112	60
p-value[a] (NA/EE or EE vs. Placebo)	--	0.2941	0.0025	0.0001	0.0001	0.0922	0.0864	0.0335	0.0001
95% Confidence Interval[b] (NA/EE or EE vs. Placebo)	--	[-1.2, ∞]	[1.3, ∞]	[4.5, ∞]	[5.2, ∞]	[-0.4, ∞]	[-0.3, ∞]	[0.2, ∞]	[2.8, ∞]
p-value[c] (Follow-up vs. Baseline)	0.0055	0.2603	0.1194	0.0001	0.0001	0.8222	0.8409	0.7170	0.0057
p-value[d] (NA/EE vs EE)	--	0.4962	0.1931	0.0006	0.2123	--	--	--	--
Month 24									
N	97	99	99	102	98	96	92	105	14
p-value[a] (NA/EE or EE vs. Placebo)	--	0.0643	0.0057	0.0001	0.0001	0.0559	0.0473	0.0049	0.1177
95% Confidence Interval[b] (NA/EE or EE vs. Placebo)		[-0.2, ∞]	[1.4, ∞]	[6.0, ∞]	[6.9, ∞]	[-0.1, ∞]	[0.0, ∞]	[1.4, ∞]	[-1.4, ∞]
p-value[c] (Follow-up vs. Baseline)	0.0019	0.6958	0.3964	0.0001	0.0001	0.8179	0.9149	0.3738	0.4798
p-value[d] (NA/EE vs EE)	--	0.9059	0.4866	0.0060	0.2255	--	--	--	--

[a] The null hypothesis is that the mean change in the NA/EE or EE treatment group is <= to the mean change in the placebo group.

[b] For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

[c] The null hypothesis is that the mean change from baseline is equal to zero.

[d] The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

Protocol 376-359
Percent Change from Baseline in Bone Mineral Density
Evaluable Data
Reference: Table 14

		NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
	Placebo	0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10
Month 12									
N	98	94	93	96	92	92	96	99	51
p-value[a] (NA/EE or EE vs. Placebo)	--	0.3162	0.0019	0.0001	0.0001	0.1976	0.0670	0.0424	0.0002
95% Confidence Interval[b] (NA/EE or EE vs. Placebo)	--	[-1.4, ∞]	[1.5, ∞]	[4.3, ∞]	[5.0, ∞]	[-0.9, ∞]	[-0.2, ∞]	[0.1, ∞]	[2.9, ∞]
p-value[c] (Follow-up vs. Baseline)	0.0019	0.1218	0.1946	0.0001	0.0001	0.2765	0.7036	0.8975	0.0163
p-value[d] (NA/EE vs EE)	--	0.7394	0.2061	0.0013	0.3189	--	--	--	--
Month 24									
N	86	86	85	89	88	81	80	90	10
p-value[a] (NA/EE or EE vs. Placebo)	--	0.1094	0.0026	0.0001	0.0001	0.0229	0.0449	0.0116	0.0826
95% Confidence Interval[b] (NA/EE or EE vs. Placebo)	--	[-0.7, ∞]	[1.9, ∞]	[5.9, ∞]	[7.1, ∞]	[0.6, ∞]	[0.1, ∞]	[1.0, ∞]	[-0.9, ∞]
p-value[c] (Follow-up vs. Baseline)	0.0002	0.1707	0.5889	0.0004	0.0001	0.7280	0.4955	0.8925	0.4445
p-value[d] (NA/EE vs EE)	--	0.4608	0.3621	0.0061	0.4805	--	--	--	--

[a] The null hypothesis is that the mean change in the NA/EE or EE treatment group is <= to the mean change in the placebo group.

[b] For difference in mean changes between the NA/EE or EE treatment group and the placebo group; 1-sided confidence interval.

[c] The null hypothesis is that the mean change from baseline is equal to zero.

[d] The null hypothesis is that the mean change in the NA/EE and corresponding EE treatment groups are equal.

Responder Analysis

The sponsor had presented a responder analysis as part of the Evaluable Analysis in the NDA. For internal consistency with the Intent-to-Treat analysis, the sponsor provided the following responder analysis in the Intent-to-Treat population: Note: Response to therapy is defined as no change or an increase from baseline BMD.

Protocol 376-359
Percentage of Patients Responding to Therapy (No Decrease from Baseline in BMD)
Months 12 and 24
All Intent-to-Treat Patients

		NA/EE Treatment Group, mg/μg				EE Treatment Group, μg			
	Placebo	0.2/1	0.5/2.5	1/5	1/10	1	2.5	5	10
Month 12									
N	112	109	115	117	112	115	118	117	99
Percent Responding	35	37	47	69	73	50	43	50	64
Month 24									
N	123	119	120	124	118	119	120	121	101
Percent Responding	24	39	39	56	66	36	38	36	62

The percentages of responders are similar to the percentages in the evaluable analysis, which was described in the NDA.

Reviewer's Comments:

Even at this conservative definition of response (i.e., no decrease from baseline in BMD), there are a modest number of responders. For the 1/5 mgNA/mcgEE treatment group, the data reveal a 56% response at 2 years in comparison to the 24% response in placebo. One might extrapolate, that the net benefit of the 1/5 mgNA/mcgEE treatment is about 30%. Alternatively, one can interpret that three to four women need to be treated in order for one to benefit from the NA/EE.

The sponsor stratified evaluable data at 24 months poststudy by years since menopause at study entry, by baseline smoking status, and by baseline physical activity level. The BMD change appeared to be larger in those who were $\geq$ 2.5 years from menopause and had never smoked. The effect of activity seemed more variable across the strata, with more BMD loss in the sedentary strata compared with the active strata. The stratifications suggest that lower doses of NA/EE and EE are required to increase or maintain BMD in patients $\geq$ 2.5 years from menopause than in patients < 2.5 years from menopause. Smoking appears to increase BMD loss and to decrease the effectiveness of both NA/EE and EE therapy in maintaining BMD.

Reviewer's Comments:

These stratifications are poststudy analyses in the evaluable data set, which has the greatest number of exclusions and represents 55% of the randomized subjects. The intent-to-treat data were not similarly stratified. Thus, the observations are of limited interest. The observations regarding response of bone mineral density to years from menopause and smoking support previous observations.

8.2.3.4.3 Safety

Comments regarding safety are based to a large extent on study 376-359, since it is the largest clinical trial with the longest duration of action. However, discussion of serious adverse events from the other trials is also included. Much of the following summary is quoted from the sponsor's Integrated Summary of Safety. Specific reviewer comments are highlighted.

Study Withdrawals

In Study 376-343, 14 FemHRT-treated subjects (6 from the 1/5 treatment group) withdrew due to symptoms or adverse events. No calcium-only-treated subject withdrew due to symptoms or adverse events. No clear pattern of events was associated with these withdrawals and integrated listing of all subjects withdrawn due to adverse events is in Appendix B.6.

When all withdrawals and withdrawals due to adverse events in Studies 376-359, -368, and -390 were integrated, the following were noted (Table 31):

- Ninety-seven FemHRT-treated subjects (10%) withdrew due to adverse events; 65 (7%) withdrew due to treatment-associated adverse events;
- Although the 2 highest dose groups had more withdrawals 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.

TABLE 31. Associated Adverse Events Leading to Withdrawal by Body System[a] (Studies 376-359, -368, and -390)

[Number (%) of Subjects]

(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Placebo		FemHRT Treatment Groups, mg NA/μg EE							
			0.2/1		0.5/2.5		1/5		1/10	
	(N = 247)		(N = 184)		(N = 244)		(N = 258)		(N = 255)	
BODY AS A WHOLE	4	(1.6)	2	(1.1)	5	(2.0)	7	(2.7)	3	(1.2)
Weight increase	2	(0.8)	1	(0.5)	1	(0.4)	3	(1.2)	0	(0.0)
Headache	1	(0.4)	1	(0.5)	2	(0.8)	4	(1.6)	1	(0.4)
Back pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Chest pain	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Edema – generalized	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)
Peripheral edema	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	2	(0.8)	2	(1.1)	1	(0.4)	3	(1.2)	3	(1.2)
Vasodilatation	1	(0.4)	2	(1.1)	0	(0.0)	0	(0.0)	2	(0.8)
Thrombophlebitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Phlebitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Thrombophlebitis deep	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Palpitation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Hypertension	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Migraine	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
DIGESTIVE SYSTEM	0	(0.0)	1	(0.5)	3	(1.2)	6	(2.3)	2	(0.8)
Mouth or throat dry	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Dyspepsia	0	(0.0)	1	(0.5)	1	(0.4)	1	(0.4)	1	(0.4)
Nausea and/or vomiting	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Constipation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Flatulence	0	(0.0)	0	(0.0)	2	(0.8)	3	(1.2)	0	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Increased appetite	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
MUSCULOSKELETAL SYSTEM	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Myalgia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
NERVOUS SYSTEM	1	(0.4)	0	(0.0)	1	(0.4)	1	(0.4)	2	(0.8)
Insomnia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	2	(0.8)
Paresthesia	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
PSYCHOBIOLOGIC FUNCTION	2	(0.8)	2	(1.1)	1	(0.4)	4	(1.6)	4	(1.6)
Depression	2	(0.8)	1	(0.5)	1	(0.4)	2	(0.8)	3	(1.2)
Nervousness	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	1	(0.4)
Emotional lability	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	2	(0.8)
Decrease/loss, libido	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	0	(0.0)	0	(0.0)	2	(0.8)	2	(0.8)	0	(0.0)
Dermatitis	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Sweating increased	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	0	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	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.

TABLE 31. Associated Adverse Events Leading to Withdrawal by Body System[a] (Studies 376-359, -368, and -390)

[Number (%) of Subjects]

(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Placebo		FemHRT Treatment Groups, mg NA/μg EE							
			0.2/1		0.5/2.5		1/5		1/10	
	(N = 247)		(N = 184)		(N = 244)		(N = 258)		(N = 255)	
UROGENITAL SYSTEM	1	(0.4)	4	(2.2)	4	(1.6)	9	(3.5)	11	(4.3)
Vaginal hemorrhage	1	(0.4)	1	(0.5)	2	(0.8)	4	(1.6)	8	(3.1)
Dysmenorrhea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Uterine polyps	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vaginal disorders	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperplasia endometrial	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)	0	(0.0)
Breast swelling	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Breast pain	1	(0.4)	0	(0.0)	2	(0.8)	3	(1.2)	3	(1.2)
Breast mass	0	(0.0)	1	(0.5)	1	(0.4)	0	(0.0)	0	(0.0)
Breast engorgement	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Premenstrual symptoms	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
TOTAL	8	(3.2)	9	(4.9)	13	(5.3)	23	(8.9)	20	(7.8)

[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.

Withdrawals due to vaginal hemorrhage appear to be dose-related ((0.4, 0.5, 0.8, 1.6, 3.1% for placebo, 0.2/1, 0.5/2.5, 1/5, 1/10 mgNA/mcgEE, respectively. Withdrawals due to breast swelling, depression, emotional lability also appear to increaase with increasing dose.

Deaths

There were 3 deaths during the clinical studies, all of which occurred during Study 376-359 (Table 29) and which were considered unlikely or definitely not related to study drug, according to the sponsor.

Listing of Deaths (Sponsor's Table has been expanded per medical officer in review of diagnoses in text.)

Treatment Group		Age	Cause of Death	Days on	Study Day	Relationship to	Narrative
Center No.	Subject No.		Investigator Term	Therapy	of Death	Study Drug	Number
Placebo							
14	18	56	Cancer Leiomyosarcoma (involving stomach and kidney)	269	610	Unlikely	D1
NA/EE 0.2/1							
62	9	56	Lung Cancer	204 (DX day 183)	216	Unlikely	D2
75	6	55	C5-6 Fracture Post Fall	0	1	Not Related	D3

Reviewer Comment: The reviewer concurs with the sponsor that the deaths are unlikely to be related to the study drug.

Endometrial hyperplasia

The incidence of endometrial hyperplasia was a primary efficacy parameter in Study 376-359.

In Study 376-359, 16 cases of endometrial hyperplasia were diagnosed by endometrial biopsy; of these, 14 were diagnosed in unopposed EE-treated subjects (10 of whom were 10 mcg EE-treated subjects; 2 were 5 mcg EE-treated; 1 was 2.5 mcg EE-treated; 1 was 1mcg EE-treated) and 1 each in placebo- and NA/EE (0.2/1)-treated subjects. The placebo-treated subject developed mild simple hyperplasia after 756 days of treatment, and the 0.2/1 FemHRT-treated subject developed hyperplasia after using a vaginal estrogen cream for 8 weeks. Duration of treatment for these subjects ranged from 99 to 756 days. After confirmation of hyperplasia, most subjects were given progestin therapy, all of which had follow-up biopsies. For all but 3 subjects, no further treatment was initiated; 2 subjects received further hormone therapy and 1 had a hysterectomy for uncontrolled bleeding. Thus, no endometrial hyperplasia was noted in the [redacted] NA/EE doses [redacted] 1/5, [redacted] mg NA mcg EE) that were originally proposed for approval. The following tables are adapted from Dr. Davis's review:

APPEARS THIS WAY
ON ORIGINAL

Summary of Endometrial Biopsies and Women with Endometrial Hyperplasia[a]

Time	Placebo	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**		**146**	**145**		**141**	**147**
N= biopsy attempts	**134**	**133**	**143**	**142**	**134**	**139**	**140**
Insufficient tissue	4	18	7	11	3	8	9
Normal 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)		**110** (75)	**109** (75)		**114** (81)	**65** (44)
N= evaluable biopsies	**83**	**69**	**65**	**71**	**90**	**94**	**61***
Insufficient tissue	30	35	45	38	20	21	6
Normal 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*
Month 24							
N= Patients biopsied (% of # randomized)	**94** (69)		**102** (70)	**99** (68)		**107** (76)	**19** (13)
N= evaluable biopsies	**59**	**57**	**65**	**65**	**67**	**90**	**18***
Insufficient tissue	35	42	37	34	23	18	2
Normal tissue	20	27	32	28	60	86	8
Atrophic tissue	38	30	33	37	6	2	0
Endometrial hyperplasia	**1**	**0**	**0**	**0**	**1[a]**	**2[a]**	**10[a]**
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.

Secondary Measures of Efficacy: Vaginal Bleeding and/or Spotting

More patients in the NAEE treatment groups reported vaginal bleeding/spotting in the earlier months of the study than patients in the EE groups. The numbers of patients in the NAEE 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 O.5/2.5 and 1/5 NAEE 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	NA mg/EE mcg			Ethinyl estradiol (EE), mcg		
		0.5/2.5	1/5	1/10	2.5	5	10[a]
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 Month 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 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)

[a]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 1 mcg EE /0.2 mg NA group and from the number of days of B/S per month are not included in this table.

Thus, the vaginal bleeding with the different mgNA/mcgEE treatment groups appeared to be dose-related, with more bleeding at the higher doses. Withdrawal from the study because of bleeding was similar for the NAEE and EE treatment groups: 2 patients withdrew from each of the 1/5 and 1 treatment arms; 8 patients withdrew from each of 1/10 and 10 treatment arms.

Papanicolaou Smear

Any abnormalities detected on Pap smears during the studies were reported as adverse events in the individual research reports. The few abnormalities reported were not dose-related.

Breast Cancer and Mammography Data

Sponsor's Summary:
A total of 9 subjects in the 4 studies were diagnosed as having breast cancer. Three cases were from Study 376-343 (all NA/EE-treated subjects) and 6 were from Study 376-359 (3 NA/EE- and 3 unopposed EE-treated subjects). These cases were distributed among 7 (3 EE and 4 NA/EE) treatment groups, and based on investigators' assessments, did not appear to be treatment-associated. Of the 9 subjects, 6 withdrew because of the breast cancer (in the NA/EE treatment groups, 2 subjects appear under "breast mass" and 2 under "breast cancer;" 2 were in EE treatment groups). One withdrew due to vaginal bleeding, and 2 completed the study prior to diagnosis. For 1 subject (10 µg EE treatment group), the breast cancer was considered by the investigator to be possibly associated with treatment. For the other 8 subjects, the relationship to drug was considered not related, unlikely, or unknown.

Listing of Subjects With Breast Cancer (Table Modified per Medical Officer to indicate Study: Study is 376-359, unless marked with * Study is 376-343))

Treatment Group Center No.	Subject No.	Age	Investigator Term/ Histopath Diagnosis	Day Began	Day Ended	Management	Relationship to Study Drug Per Sponsor	Outcome	Narrative Number
0.2/1 NA/EE									
5	1	50	Breast Cancer/Infiltrating Carcinoma; Intraductal Carcinoma	201[a]	Cont	None	Unlikely	Unknown	S21[b]
0.5/2.5 NA/EE									
40	6	53	Right Breast Mass - Malignant/Infiltrating Ductal Carcinoma	143	Cont	Discontinued	Unknown	Not Yet Recovered	BC1
1/5 NA/EE									
48	11	49	Metastatic Breast Cancer/Unknown	552[a]	Cont	Discontinued	Unknown	Not Yet Recovered	BC2
1*	51	54	Breast Cancer/Intraductal Carcinoma	1487	Unknown	Discontinued	Unlikely	Recovered	BC3
0.5/10 NA/EE									
1*	18	57	Precancerous Lesions – Left Breast	Unknown	Unknown	Unknown	Unknown	Unknown	BC4
1/10 NA/EE									
36	17	57	Suspicious for Breast Cancer/Invasive Lobular Carcinoma; Intraductal Carcinoma; Lobular Carcinoma In Situ	393	Cont	Discontinued	Unlikely	Not Yet Recovered	BC5
*	73[c]	47	Breast Cancer/Infiltrating Ductal Carcinoma	773	Cont	Discontinued	Not Related	Not Yet Recovered	BC6
1 EE									
61	11	54	Cancer of Right Breast/Infiltrating Tubular Ductal Carcinoma	714	777	None	Unlikely	Recovered/Sequelae	BC7
2.5 EE									
60	20	53	Breast Cancer/Infiltrating Carcinoma; Lobular Carcinoma	380	410	Discontinued	Not Related	Recovered/Sequelae	BC8
10 EE									
29	5	53	Breast Cancer/Ductal Carcinoma; Intraductal Carcinoma In Situ	367	Cont	None	Possibly	Not Yet Recovered	BC9

[a] Estimated study day, complete date not provided; patient (completed) withdrew from study on day 114 and breast cancer was noted 87 days later. (underlined comment added per medical officer)
[b] Identified 87 days after completing study; narrative in Appendix B.5 with serious adverse event narratives.
[c] Subject was randomized to the 1/20 treatment group that was terminated after Year 1; she was rerandomized to the 1/10 treatment group for the remainder of the study.

The number of breast cancer cases observed in the NA/EE treatment groups (6) was compared to the number expected based on the accumulated subject time on drug in these studies and the incidence of breast cancer in the National Cancer Institute's Surveillance, Epidemiology, and End Results (NCI-SEER) Program. The NCI-SEER data are based on a sample of 10% of the United States' population.

The resulting standardized mortality ratio (SMR equals observed number of cases/expected number of cases) is 1.98 with an exact 95% confidence interval of (0.72, 4.31). The value of 1 is within this interval, and thus the cases observed among NA/EE-treated subjects are not significantly different from the expected 2.94 cases.

Reviewer's Comments: **There are actually 7 reports of breast cancer in women who took NA/EE: 4 participated in Study 376-359 and 3 participated in Study 376-343. In addition there are 3 reports of breast cancer in women who took EE who participated in Study 376-359. No cases of breast cancer were reported in women taking placebo. The resulting standardized mortality ratio is higher than calculated above by the sponsor, though the seventh patient withdrew from the study on day 114 and thus contributed a small amount of observation time. This comparison to a standardized incidence such as the NCI-SEER provides an overview of risk but it does not account for specific risk factors in the patients, such as family history, early menarche, late menopause, parity status, or prior use of estrogen. Although it is difficult to assign causation on the basis of 7/631 patients exposed to NA/EE in studies 376-343 and 376-359. However, this reviewer would not agree with the sponsor's and/or investigator's assessment that there is no relationship between breast cancer and NA/EE.**

In a metaanalysis of breast cancer and hormone replacement based on 160 000 women who participated in 51 epidemiological studies over 25 years, an increased relative risk of breast cancer among current or recent users of HRT for more than 5 years was noted. (Collaborative Group on Hormonal Factors in Breast Cancer, Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108411 women with out breast cancer, Lancet , Vol. 350, 1047-1059, 1997) In that report, the authors noted that only 12% of the hormone users had been exposed to progestagens and that the conclusions regarding the combination could not be drawn.

Mammograms were performed at baseline and Years 1 and 2 for Study 376-359, at baseline and Years 1 to 5 for Study 376-343, and at baseline only for Studies 376-368 (16-week study) and 376-390 (12-week study). Approximately half of all subjects in Study 376-359 showed some mammographic abnormality prior to treatment, mostly fibrocystic changes, calcification, and density. The pattern of abnormalities was maintained while subjects received treatment and there was not any shift in preponderance of abnormality by treatment. None of the active treatment groups differed from the placebo treatment group in frequency or type of abnormality noted before or during treatment. There did not appear to be any dose-related effect on mammographic abnormalities.

Other Cancers

Eighteen subjects in Study 376-359 were diagnosed with cancer other than breast cancer: 10 were treated with FemHRT, 6 with EE, and 2 with placebo, suggesting no dose- or treatment-related pattern. There was no apparent relation between time in study and diagnosis of cancer (Study Days 6 to 694). Fourteen cases of cancers were considered definitely not related to treatment, and 4 unlikely.

The types of cancer were basal cell (6 subjects), ovarian (3), colon (2), and lung (2); and 1 each of tongue, squamous cell, skin, cervical, and sarcoma. The 3 ovarian cancers were diagnosed in patients on NA/EE:

Patients with Ovarian Cancer		
Treatment (mg NA/mcgEE)	Age of patient	Day of diagnosis (day of study)
.2/1	56	518
.2/1	51	814
1/5	55	79

One basal cell carcinoma was diagnosed in a patient on placebo on day 694.

Effects of FemHRT on the Lipid Profile

The effect on the lipid profile was considered a secondary efficacy parameter in the study 376-359. It was also considered a safety issue in terms of possible deterioration of the lipid profile with the addition of a progestin. The protocol was designed to look at changes in the lipid profiles in the treatment groups in comparison to placebo, but it was not designed for multiple comparisons between groups. The sponsor's table below supports the safety profile of NAEE vis a vis the effects on lipids. There is no deterioration in the lipid profile in comparison to that seen in the EE groups alone. The mean baseline total cholesterol ranged from 212 to 222 mg/dl and the mean triglyceride ranged from 99 to 114 mg/dl.

TABLE 4. Mean Change From Baseline Lipid Profile. Values After 2 Years of Treatment With FemHRT

Lipid Parameter	Placebo	FemHRT (mgNA/μgEE)			EE (μg)		
		0.5/2.5	1/5	1/10	2.5	5	10
	N = 129	N = 128	N = 132	N = 129	N = 126	N = 128	N = 127
Total Cholesterol[a] (mg/dL)	2.5	-12.5	-16.6	-3.7	0.3	3.4	4.7
HDL-C[a] (mg/dL)	0.1	-1.1	-4.8	-0.7	5.7	9.9	5.4
LDL-C (mg/dL)	0.6	-12.1	-12.3	-6.3	-9.7	-11.4	-5.6
Triglycerides[a] (mg/dL)	14.1	2.7	3.0	20.8	22.0	30.4	32.6
Total Cholesterol/HDL-C	0.052	-1.99	0.013	-0.048	-0.33	-0.479	-0.274

NA = Norethindrone acetate.
EE = Ethinyl estradiol.
[a] Each NA/EE treatment combination group differs significantly ($p < 0.05$) from matching unopposed EE group.

Thromboembolic Adverse Events

In the clinical studies, 6 of all 1006 FemHRT-treated subjects (0.6%) experienced thromboembolic events; these are summarized in Table 28.

TABLE 28. Thromboembolic Adverse Events
(Note: Patient age, Treatment Group Assignment, Study Day of Diagnosis Added per Medical Officer.)

Study Number	Number (%[a]) of Subjects		Event (Incidence)	Patient Age	NA/EE Mg/mcg Day
376-343	2	(0.2)	DVT (1)	54	1/10 906
			Thrombophlebitis (1)	54	1/20 39
376-359	3	(0.3)	DVT (1)	57	1/5 588
			Superficial Phlebitis (1)	51	1/10 509
			Possible CVA (1)	61	.2/1 180
376-390	1	(0.1)	Superficial Thrombophlebitis (1)	56	1/5 40

DVT = Deep vein thrombosis; CVA = Cerebral vascular accident; TIA = Transient ischemic attack.
[a] Percent of all FemHRT-treated subjects (1006).

Reviewer's comment: All the thromboembolic events occurred on the NA/EE treatment arms. All women were current or past smokers. No thromboembolic events were described in patients taking placebo.

General Symptoms

Breast pain, generalized edema, and headache are the most common adverse events associated with NA/EE treatment, and appear to be dose-related. Three of the symptoms usually associated with HRT; headache, nausea/vomiting, and breast pain, are reported by more NA/EE -treated subjects, especially at the highest dose, than by calcium-only- or placebo-treated subjects. Abdominal pain is also more common with NA/EE than with placebo.

TABLE 17. Adverse Events Reported by ≥5% of Subjects by Body System[a] (Study 376-359)

[Number (%) of Subjects]

(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Placebo	FemHRT Treatment Groups, mg NA/μg EE			
		0.2/1	0.5/2.5	1/5	1/10
	N = 137	N = 139	N = 136	N = 146	N = 145
BODY AS A WHOLE	71 (51.8)	68 (48.9)	66 (48.5)	73 (50.0)	77 (53.1)
Headache	26 (19.0)	22 (15.8)	25 (18.4)	35 (24.0)	39 (26.9)
Viral Infection	14 (10.2)	19 (13.7)	15 (11.0)	16 (11.0)	14 (9.7)
Back Pain	9 (6.6)	10 (7.2)	11 (8.1)	9 (6.2)	13 (9.0)
Edema - Generalized	9 (6.6)	11 (7.9)	10 (7.4)	9 (6.2)	12 (8.3)
Pain	10 (7.3)	8 (5.8)	7 (5.1)	4 (2.7)	12 (8.3)
Allergy	8 (5.8)	5 (3.6)	5 (3.7)	7 (4.8)	6 (4.1)
Weight Increase	10 (7.3)	10 (7.2)	6 (4.4)	5 (3.4)	6 (4.1)
Fever	2 (1.5)	1 (0.7)	7 (5.1)	3 (2.1)	2 (1.4)
CARDIOVASCULAR SYSTEM	27 (19.7)	21 (15.1)	18 (13.2)	22 (15.1)	19 (13.1)
Vasodilatation	19 (13.9)	7 (5.0)	4 (2.9)	3 (2.1)	9 (6.2)
Hypertension	7 (5.1)	7 (5.0)	7 (5.1)	8 (5.5)	7 (4.8)
DIGESTIVE SYSTEM	39 (28.5)	58 (41.7)	50 (36.8)	55 (37.7)	55 (37.9)
Nausea and/or Vomiting	10 (7.3)	12 (8.6)	10 (7.4)	14 (9.6)	13 (9.0)
Abdominal Pain	5 (3.6)	14 (10.1)	19 (14.0)	16 (11.0)	12 (8.3)
Constipation	10 (7.3)	12 (8.6)	6 (4.4)	8 (5.5)	10 (6.9)
Diarrhea	5 (3.6)	9 (6.5)	10 (7.4)	7 (4.8)	8 (5.5)
Flatulence	3 (2.2)	12 (8.6)	5 (3.7)	5 (3.4)	8 (5.5)
Dyspepsia	4 (3.9)	8 (5.8)	12 (8.8)	7 (4.8)	6 (4.1)
Dental Abnormalities	6 (4.4)	11 (7.9)	4 (2.9)	9 (6.2)	7 (4.8)
MUSCULOSKELETAL SYSTEM	37 (27.0)	39 (28.1)	30 (22.1)	33 (22.6)	32 (22.1)
Myalgia	16 (11.7)	16 (11.5)	15 (11.0)	13 (8.9)	11 (7.6)
Arthralgia	12 (8.8)	14 (10.1)	6 (4.4)	13 (8.9)	8 (5.5)
NERVOUS SYSTEM	17 (12.4)	15 (10.8)	17 (12.5)	21 (14.4)	19 (13.1)
Paresthesia	3 (2.2)	4 (2.9)	7 (5.1)	3 (2.1)	4 (2.8)
PSYCHOBIOLOGIC FUNCTION	12 (8.8)	11 (7.9)	9 (6.6)	21 (14.4)	19 (13.1)
Depression	8 (5.8)	3 (2.2)	5 (3.7)	11 (7.5)	9 (6.2)
RESPIRATORY SYSTEM	55 (40.1)	55 (39.6)	55 (40.4)	60 (41.1)	58 (40.0)
Rhinitis	30 (21.9)	24 (17.3)	24 (17.6)	26 (17.8)	27 (18.6)
Sinusitis	19 (13.9)	23 (16.5)	20 (14.7)	19 (13.0)	19 (13.1)
Upper Respiratory Infection	7 (5.1)	8 (5.8)	8 (5.9)	10 (6.8)	15 (10.3)
Pharyngitis	6 (4.4)	5 (3.6)	5 (3.7)	6 (4.1)	8 (5.5)
Coughing	6 (4.4)	9 (6.5)	10 (7.4)	7 (4.8)	5 (3.4)
Bronchitis	4 (2.9)	8 (5.8)	10 (7.4)	8 (5.5)	7 (4.8)

[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.

TABLE 17. Adverse Events Reported by ≥5% of Subjects by Body System[a] (Study 376-359)

[Number (%) of Subjects]

(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Placebo		FemHRT Treatment Groups, mg NA/μg EE							
			0.2/1		0.5/2.5		1/5		1/10	
	N = 137		N = 139		N = 136		N = 146		N = 145	
SKIN AND APPENDAGES	28	(20.4)	27	(19.4)	29	(21.3)	39	(26.7)	31	(21.4)
Rash	2	(1.5)	5	(3.6)	3	(2.2)	9	(6.2)	8	(5.5)
Acne	1	(0.7)	5	(3.6)	7	(5.1)	7	(4.8)	3	(2.1)
UROGENITAL SYSTEM	41	(29.9)	55	(39.6)	54	(39.7)	68	(46.6)	67	(46.2)
Breast Pain	11	(8.0)	15	(10.8)	19	(14.0)	20	(13.7)	30	(20.7)
Vaginitis	11	(8.0)	8	(5.8)	11	(8.1)	13	(8.9)	13	(9.0)
Vaginal Hemorrhage	0	(0.0)	1	(0.7)	4	(2.9)	2	(1.4)	9	(6.2)
Urinary Tract Infection	6	(4.4)	12	(8.6)	9	(6.6)	14	(9.6)	7	(4.8)
Leukorrhea	5	(3.6)	4	(2.9)	10	(7.4)	5	(3.4)	5	(3.4)
Vaginal Disorders	7	(5.1)	6	(4.3)	2	(1.5)	1	(0.7)	1	(0.7)

[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.

The most frequent adverse events reported by NA/EE-treated subjects in Studies 376-359, -368, and -390 combined were headache (18%), rhinitis (15%), and breast pain (11%) (Table 20). 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 NA/EE treatment group.

APPEARS THIS WAY
ON ORIGINAL

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

	[Number (%) of Subjects]									
BODY SYSTEM/ Adverse Event	Placebo		FemHRT Treatment Groups, mg NA/μg EE							
			0.2/1		0.5/2.5		1/5		1/10	
	N = 247		N = 184		N = 244		N = 258		N = 255	
BODY AS A WHOLE	99	(40.1)	86	(46.7)	94	(38.5)	102	(39.5)	112	(43.9)
Headache	36	(14.6)	30	(16.3)	37	(15.2)	47	(18.2)	52	(20.4)
Back Pain	13	(5.3)	12	(6.5)	13	(5.3)	12	(4.7)	16	(6.3)
Pain	11	(4.5)	9	(4.9)	9	(3.7)	10	(3.9)	14	(5.5)
Viral Infection	19	(7.7)	24	(13.0)	21	(8.6)	18	(7.0)	24	(9.4)
Edema-Generalized	12	(4.9)	16	(8.7)	12	(4.9)	12	(4.7)	14	(5.5)
DIGESTIVE SYSTEM	44	(24.4)	63	(34.2)	54	(30.5)	63	(33.0)	68	(35.8)
Nausea and/or Vomiting	13	(5.3)	13	(7.1)	13	(5.3)	19	(7.4)	23	(9.0)
Abdominal Pain	11	(4.5)	15	(8.2)	25	(10.2)	21	(8.1)	18	(7.1)
Dental Abnormalities	8	(3.2)	12	(6.5)	6	(2.5)	12	(4.7)	9	(3.5)
Dyspepsia	5	(2.0)	8	(4.3)	13	(5.3)	8	(3.1)	9	(3.5)
Diarrhea	9	(3.6)	9	(4.9)	14	(5.7)	10	(3.9)	11	(4.3)
Flatulence	4	(1.6)	12	(6.5)	6	(2.5)	6	(2.3)	11	(4.3)
Constipation	10	(4.0)	13	(7.1)	6	(2.5)	8	(3.1)	13	(5.1)
MUSCULOSKELETAL SYSTEM	39	(21.7)	47	(25.5)	36	(20.3)	39	(20.4)	39	(20.5)
Arthralgia	17	(6.9)	15	(8.2)	7	(2.9)	15	(5.8)	9	(3.5)
Myalgia	21	(8.5)	20	(10.9)	21	(8.6)	20	(7.8)	21	(8.2)
PSYCHOBIOLOGIC FUNCTION	15	(8.3)	15	(8.2)	14	(7.9)	27	(14.1)	25	(13.2)
Nervousness	4	(1.6)	3	(1.6)	4	(1.6)	14	(5.4)	7	(2.7)
Depression	9	(3.6)	4	(2.2)	9	(3.7)	15	(5.8)	15	(5.9)
RESPIRATORY SYSTEM	67	(37.2)	63	(34.2)	60	(33.9)	68	(35.6)	67	(35.3)
Rhinitis	38	(15.4)	29	(15.8)	31	(12.7)	39	(15.1)	39	(15.3)
Sinusitis	24	(9.7)	24	(13.0)	23	(9.4)	21	(8.1)	25	(9.8)
Upper Respiratory Infection	11	(4.5)	9	(4.9)	10	(4.1)	10	(3.9)	17	(6.7)
Coughing	9	(3.6)	11	(6.0)	10	(4.1)	9	(3.5)	6	(2.4)
UROGENITAL SYSTEM	45	(25.0)	62	(33.7)	56	(31.6)	78	(40.8)	79	(41.6)
Breast Pain	13	(5.3)	18	(9.8)	23	(9.0)	21	(8.1)	43	(16.9)
Urinary Tract Infection	8	(3.2)	14	(7.6)	9	(3.7)	16	(6.2)	7	(2.7)
Vaginitis	12	(4.9)	8	(4.3)	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 more than one AE per body system.

Blood Pressure

Study 376-343 evaluated angiotensinogen levels and hemolytic/coagulation factors. Results for angiotensinogen are available only for Years 1 and 2 of the study and hemolytic/coagulation factor results for Years 1 through 4.

Mean baseline angiotensinogen levels were similar across treatment groups. In the active treatment groups, including MPA/CEE, angiotensinogen levels increased markedly by Month 6, and by Month 12 and Year 2 mean angiotensinogen levels were approximately 1 to 3 times greater than baseline levels. The calcium-only group exhibited small changes from baseline. Angiotensinogen was not measured in any of the other clinical studies.

Overall, in all 4 clinical studies, there were no clinically significant differences in blood pressure between active- and placebo- treated subjects. Furthermore, despite the increases in

angiotensinogen observed in Study 376-343 (see Section 7.4.1), mean blood pressure was not affected by HRT at any time during the 5-year study. In addition, a review of individual blood pressure measurements identified no hypertension.

Mean changes and mean percent changes from baseline in blood pressure were similar across all treatment groups in Study 376-359 with slight increases in most of the groups, except for the 0.2/1 FemHRT group where both systolic and diastolic blood pressure decreased slightly. It should be noted that this group had the highest baseline mean blood pressure. Similarly, the largest increase in blood pressure was observed in the 1/5 FemHRT treatment group; this group had the lowest baseline mean blood pressure.

Approximately 14% of FemHRT-treated subjects had an increase or decrease in systolic and/or diastolic blood pressure of >30% from baseline. Although there appears to be a trend for more subjects to have >30% increases from baseline in blood pressure with increasing doses of FemHRT, the observed changes are not unexpected for this subject cohort.

Two percent of subjects had increased blood pressure that was considered by the investigator to be associated with study medication. No serious adverse events of increased blood pressure were reported. Five subjects withdrew from the study due to increases in blood pressure.

Abdominal Pain and Gallbladder Disease

Abdominal pain was a common adverse event across all treatment groups with 7-10% of the NA/EE groups reporting abdominal pain as compared to 4.5% of the placebo group. There was no increase of reported abdominal pain with increased dose. In all 4 studies, 3 of all FemHRT-treated subjects (0.3%) had adverse events related to the gallbladder. Two subjects in Study 376-359, one 1/5 FemHRT-treated subject and one 1/10 FemHRT-treated subject, presented with right upper quadrant pain and, subsequently, each had a cholecystectomy. The gallbladder pain for each woman was considered possibly related to treatment. Both subjects completed the study. One subject in Study 376-343 (0.5/10 FemHRT) with a history of cholecystitis withdrew. Further studies would be needed to assess if the increased reporting of abdominal pain with NA/EE may be related to subclinical gall bladder disease.

Fractures

The sponsor did not rigorously assess fractures at baseline or subsequently. There were no baseline or followup lumar spine x-rays. The population studied had normal bone mineral density for their age group, and thus fractures are really not expected. The sponsor lists the following vertebral bodies that were excluded due to crush fracture. Note fractures were observed in only 6 out of 1265 enrolled subjects. In the adverse events section, there are four fractures listed (C5-C6, ankle, knee, and vertebrae), all of which are associated with trauma.

Exclusions of Crush Fracture Vertebral Bodies from CT Scan Averages (*Adapted from Appendix C1 CT Exclusions, page 1) (*Added per Medical Officer)				
Center	Patient Number	*Treatment Group	Study Day	Vertebral Body
1	8	1/10 mgNA/mcgEE	452	L2
8	18	1/10 mgNA/mcgEE	322	L5
8	18	1/10 mgNA/mcgEE	733	L5
20	3	0.5/2.5 mgNA/mcgEE	341	L2
37	17	1 mcg EE	-42	L5
61	4	1 mcg EE	-8	L4
61	4	1 mcg EE	-8	L5
80	17	2.5 mcg EE	335	L2

9. Overview of Efficacy and Safety Conclusions

This NDA supports the approval of the 1/5 mgNA/mcgEE dose for prevention of osteoporosis in postmenopausal women with intact uteri. Since this population did not include women with osteoporosis, there is no indication for the treatment of osteoporosis. From discussions with the Division of Reproductive and Urologic Drug Products (HFD-580), this dose selection also coincides with their selection of this dose for endometrial protection and vasomotor symptoms. From a regulatory perspective, the one large multicenter 2-year study with bone mineral density as the endpoint meets the criteria established in the "Draft Osteoporosis Guidance" and the "Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women" for the prevention of osteoporosis indication with an estrogen. This dose selection provides efficacy in the prevention of osteoporosis for postmenopausal women who are relatively newly postmenopaual (mean 31 months post menopausal) and have intact uteri and is balanced by a tolerable risk profile. Specifically, the dose is associated with a modest prevalence of vaginal bleeding (24% of the women using 1/5 vs 34% of the women using 1/10 had vaginal bleeding at 1 year; 12 % of the women using 1/5 and 11% of the women using 1/10 had persistent vaginal bleeding at 2 years), breast tenderness, headaches. The lipid profile improves with NA/EE therapy. There may be a slight excess of cancer – particularly breast and ovarian cancers associated with the use of NA/EE, though this data set is too small to reach these conclusions. There is also a small increased risk of thromboembolic events associated with the use of NA/EE.

The following general comments place this treatment in perspective and are themes that can be emphasized in the labeling.

(1) The selected patient population is relatively young, healthy, and does not have osteoporosis. It probably represents a relatively healthier subset of the target population of postmenopausal women who seek therapy for prevention of osteoporosis. Thus, one might expect a greater number of adverse events in a less healthy population, which may include women with treated hypertension and diabetes mellitus.

(2) The population studied in the NDA did not receive adequate calcium and vitamin D supplementation. The lack of adequate calcium and vitamin D supplementation may contribute to the large treatment effect seen. This label, however, recommends adequate calcium and vitamin D supplementation.

(3) Only lumbar vertebrae bone mineral density was measured. Review of the literature does not suggest any deleterious effects of norethindrone acetate on appendicular bone.

(4) Heights at the end of the study were not reported in the NDA. Therefore, there is no independent clinical assessment that prevention of osteoporosis helped preserve height.

(5) There is no systematic fracture data, though one would not expect many fractures in a population that has a normal bone mineral density for its age.

(6) In the sponsor's randomized clinical trial ("CHART" study), there were numerous entry exclusions that the sponsor probably does not plan to exclude in the target population. Thus there is little information regarding the following conditions that were excluded: e.g., women with vasomotor symptoms requiring therapy were excluded from the longer BMD studies and were only included in the shorter term 12-16 week hot flash frequency and intensity studies; women with hypertension, hypercholesterolemia and/or diabetes mellitus; women with established osteoporosis.

(7) Since the [redacted] was withdrawn, there is no recommended [redacted] in the label. It is conceivable that women close to menopause (such as this population – 31 months post menopause) may require a relatively higher estrogen dosage to control vasomotor symptoms. As they get older, a lower estrogen replacement may be adequate for maintenance of bone density. This concept is a speculation, as there are no appropriate supportive data in this trial where older women with osteoporosis were not studied. However, this trend has been supported by other studies. Thus, it is important for the individual postmenopausal woman and her healthcare provider to continue to assess efficacy of the drug product in maintaining efficacy in the prevention of osteoporosis and diminution of vasomotor symptoms and safety with regular breast exams, Pap smears, and general health followup.

(8) For comparison with other estrogen products, the efficacy of 5 mcg EE on biochemical and biological markers appears to compare to the efficacy of 0.625 mg conjugated equine estrogen. (Mandel FP, Geola FL, Lu JK, Eggena P, Sambhi MP, Hershman JM, Judd HL Biologic Effects of various doses of ethinyl estradiol in postmenopausal women. Obstet Gynecol 59:673-9,1982.) No similar comparison is available for the effect on bone mineral density. The NA contributes an additional 2.8 mcg EE through its metabolism. The comparative information of different estrogen preparations, though based on a limited database, may be important to include in the physician's label.

10. Labeling Recommendations

Labeling Recommendations – **Division of Metabolic and Endocrine Drug Products**
9/27/99 – Revised 9/30/99 after withdrawal of [redacted] by sponsor

Specific recommendations for the physician label for norethindrone acetate/ethinyl estradiol regarding the osteoporosis indication are listed below. In addition, several recommendations regarding nomenclature are also made. Page numbers refer to page numbers in the physician package insert, as submitted in Volume 1 of the NDA. We have just received a copy of the currently updated label forwarded by the sponsor to the Division of Reproductive and Urologic Drug Products and we will be discussing additional changes with them internally.

CHANGE	REASON
Page 13 of 32: Delete [redacted]	Reference to the name [redacted] has been removed from the label by HFD-580. An acronym in the label may confuse the clinician. A more specific description of the studied population provides the clinician with a

	clearer, potentially more applicable reference to a patient the clinician may choose to treat with the drug.
Page 13 of 32: Insert "A total of 283 postmenopausal women with intact uteri and normal baseline bone mineral density (mg/cc) were randomized to FemHRT 1/5 **mg** morethindrone acetate/**mcg** ethinyl estradiol and placebo, and 87% contributed data to the Intent-To-Treat analysis. All patients received 1000 mg calcium in divided doses. Vitamin D was not supplemented." APPEARS THIS WAY ON ORIGINAL	A more specific description of the studied population provides the clinician with a clearer, potentially more applicable reference to a patient the clinician may choose to treat with the drug. *Comments to sponsor*: (1) Please supply the correct baseline BMD for this randomized population (1/5 (**mg** norethindrone acetate/**mcg** ethinyl estradiol) dose and placebo). (2) (3) Since the sponsor has deleted the dose from the NDA, it is omitted also from this section. (4) Please print in **bold "mg" and "mcg" to minimize confusion about the dosages of** norethindrone acetate/ ethinyl estradiol (5) The low supplementation with calcium and absence of vitamin D supplementation may partially explain the BMD loss in the placebo group.
Page 13 of 32: *Insert* "(**mg** norethindrone acetate/**mcg** ethinyl estradiol)" after FemHRT	The inclusion of this description minimizes confusion about the relative contributions of the progestogen and estrogen in this combination.
Page 14 of 32: *Delete*	(1) The original protocol was designed to compare the BMD of each treatment group to placebo. The original protocol was not designed to account for multiple comparisons of different treatment groups. (2) The EE treatment arms are not mentioned in this section. (3) Including this reference is confusing to the clinician, particularly since ethinyl

	estradiol does not have an osteoporosis indication.
Page 14 of 32: *Please note the following inserted comment:* [*Note to sponsor*: Please change ordinate label to "Percent Change in Lumbar Spine Bone Mineral Density from Baseline (+SE)" and change table accordingly. The [redacted] doses should be removed from the table.]	(1) Quantitative computerized tomography is often used in research studies, but less commonly used in clinical practice. Clinicians may not be familiar with the units. (2) Other labels for drugs with the osteoporosis indication depict "percent change." We understand that the sponsor's primary efficacy for BMD was change in BMD and not percent change in BMD. However, we are trying to maintain consistency across labels to simplify the message for the practicing clinician. (3) Inclusion of doses not approved for osteoporosis would be confusing to the clinician.
Page 14 of 32: *Please note the following modified figure legend:* FIGURE 4. Percent Change in Lumbar Spine Bone Mineral Density ±SE) From Baseline at Month 12 and Month 24	Title of figure should reflect the presented data.
Page 14 of 32: *Please note the following inserted comment:* [*Note to Sponsor:* Data presented should be based on Intent to Treat Analysis with Last Observation Carried Forward.]	For consistency in the osteoporosis label, the FDA statisticians have recommended the depiction of the Intent To Treat analysis in the label, as this analysis is preferred by the FDA. Please see "E9 Statistical Principles for Clinical Trials", Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98 Please also submit a copy of the Intent-to-Treat Analysis at 12 months for FDA review, as it was not included in the NDA.
<u>General change:</u> Order of active ingredient presentation as NA/EE.	The Division of Metabolic and Endocrine Drug Products understands that the sponsor has discussed this issue with the Division of Reproductive and Urologic Drug Products. However, we must comment, as we too feel that placing the progestogen before the estrogen has a precedent in a drug marketed for oral contraception but not in a drug marketed for osteoporosis. The change in the order of

	the estrogen and progestogen, particularly since there is a 1000 fold difference between the estrogen and progesterone dosage strengths though the actual numbers are of the same order of magnitude, could be misleading to the clinician.
General change: Change of Proposed Trade Name **FemHRT**	The Division of Metabolic and Endocrine Drug Products finds this trade name potentially misleading to the clinician because of the possible implication of "heart" from "HRT". (1) Current data regarding the cardiac protective effects of estrogen are still controversial. (2) This NDA was not designed with lipids as a primary efficacy outcome. In general, it is still controversial whether the improvement seen in the lipid profile with estrogen therapy confers a benefit. (3) In addition, the 'HRT' acronym is a common abbreviation for hormonal replacement therapy which may be also potentially misleading to clinicians.

10/4/99

Additional labeling recommendations are listed regarding the osteoporosis section, which evolved after discussion of the general physician label with the Division of Reproductive and Urologic Drug Products today:

Change	**Comment**
Pages 14-15 (Indications and Usage) *Please delete the following sections*	The goal of these changes is simplification and greater clarity of the label.

	APPEARS THIS WAY ON ORIGINAL
	Please add "postmenopausal" and "vitamin D"
	Please add "and adequate daily intake of vitamin D (400 IU)".

Page 27 (Dosage and Administration) *Delete* *Add:* "Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding. Patients should be evaluated at least annually for breast abnormalities and more often if there are any symptoms."	Rather than suggest evaluation of efficacy to the caregiver, the emphasis is safety. APPEARS THIS WAY ON ORIGINAL

Further discussion between the sponsor and FDA resulted in a change of the trade name to femhrt as of 10/6/99. In a Telecon between Division of Metabolic and Endocrine Drug Products (DMEDP) and the sponsor on 10/7/99, the sponsor agreed to all the labeling changes except the withdrawal of the DMEDP reiterated the

11. Recommendations

Approval of the 1/5 norethindrone acetate ethinyl estradiol (mgNA/mcgEE) dosage for the indication of prevention of postmenopausal osteoporosis in women with intact uteri, pending

1) adequate final sponsor responses to FDA questions;
2) change in labeling, as requested by FDA.

Possible approval of the norethindrone acetate ethinyl estradiol (mgNA/mcgEE) for the indication of if appropriate labeling is included that this

/S/
Joanna K. Zawadzki, M.D., F.A.C.P.

/S/ 10/15/99

Concurrence:

Gloria Troendle, M.D.
Team Leader
Medical Officer Review

Distribution:
Archival:HFD580/NDA21-065
HFD510/Sobel/Troendle/Hoberman/Galliers/Zawadzki

SELECTED REFERENCES:

Cann CE, Genant HK, Kolb FO, Ettinger B Quantitative Computed Tomography for Prediction of Vertebral Fracture Risk, Bone 6: 1-7, 1985

Collaborative on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet 350: 1047-1059, 1042-1044, 1997

Draft Osteoporosis Guidance: "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis", 1994

E9 Statistical Principles for Clinical Trials, Federal Register, Vol. 63, No. 179, 49583-98, 9/16/98

Genant HK et al (Estratab/Osteoporosis Study Group). Low-Dose Esterified Estrogen Therapy. Arch Intern Med 157: 2609-2615, 1997

Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women, 1995

Hulley S et al (Heart and Estrogen/progestin Replacement Study (HERS) Research Group). Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. JAMA 280:605-613, 1998

Kalendar WA, Felsenberg D, Louis O, Lopez P, Klotz E, Osteaux M, Fraga J. Reference Values for Trabecular and Cortical Vertebral Bone Density in Single and Dual-Energy Computed Tomography, Europ J Radiol 9: 75-80, 1989

Mandel FP, Geola FL, Lu JK, Eggena P, Sambhi MP, Hershman JM, Judd HL Biologic Effects of various doses of ethinyl estradiol in postmenopausal women. Obstet Gynecol 59:673-9,1982.

Pettiti D. Hormone Replacement Therapy and Heart Disease Prevention: Experimentation Trumps Observation. JAMA 280: 650-652, 1998

The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. JAMA 275: 370, 1996