

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 21040**

**MEDICAL REVIEW(S)**

NDA 21-040

Medical Officer's Review

<sup>1</sup>OCT 22 1999

NDA 21-040

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Medical Officer's Review  
(Original Review)

Sponsor: The R. W. Johnson Pharmaceutical Research Institute

Drug Name:

Generic: 17 $\beta$ -Estradiol Tablet and  
17 $\beta$ -Estradiol plus Norgestimate Tablets  
Trade: Ortho-Prefest™  
Chemical: 17 $\beta$ -Estradiol, USP  
Estra-1, 3, 5(10)-triene-3,17-diol, (17 $\beta$ )-diol  
Norgestimate  
(17 $\alpha$ )-17-(acetyloxy)-13-ethyl-18, 19-dinorpregn-4-en-20-yn-3-one  
3-oxime

Route: Oral

Dosage Form: Tablet

Strength: 1mg 17 $\beta$ -Estradiol  
1mg 17 $\beta$ -Estradiol plus 90  $\mu$ g Norgestimate

Proposed Indications: 1) Treatment of moderate to severe vasomotor symptoms.  
2) Treatment of vulvovaginal atrophy.  
3) The prevention of osteoporosis.

Related Submissions: IND  
NDA 19-697 and NDA 19-653

Related Documents:

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## 1. Resume

This 288 volume NDA, submitted by The R. W. Johnson Pharmaceutical Research Institute on December 23, 1998, for cyclophasic hormone replacement therapy (CHRT) with 1 mg of 17 $\beta$ -estradiol (E<sub>2</sub>) and 1 mg of 17 $\beta$ -estradiol (E<sub>2</sub>) + 90  $\mu$ g norgestimate (NGM) contains three pivotal Phase III controlled safety and efficacy studies (ESTNRG-CHRT-102 and 103, cyclophasic HRT, have data pooled and presented as one study; and ESTNRG-CHRT-104, estradiol-alone), and three supportive studies (N93-072, CC2636-C-101, and ESTNRG-CHRT-105) in support of the treatment of vasomotor symptoms, treatment of vulvovaginal atrophy, and the prevention of endometrial hyperplasia. The dosage regimen for the two pivotal cyclophasic HRT studies and the three supportive studies was continuous estradiol treatment combined with intermittent progestin treatment given in a 3-days-on and 3-days-off schedule.

The prevention of osteoporosis indication is supported by two bioequivalence studies. ESTNRG-PHI-006 compared the sponsor's 0.5 mg E<sub>2</sub> tablet to Estrace®, and ESTNRG-PHI-007 compared the 1 mg E<sub>2</sub> tablet to Estrace®. One drug interaction study, ESTNRG-PHI-001 provides information on the single- and multiple-dose pharmacokinetics of E<sub>2</sub>, NGM, and their metabolites in postmenopausal women receiving continuous 1 mg E<sub>2</sub> and intermittent 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90  $\mu$ g NGM given in a 3-day-on and 3-day-off schedule.

At a pre-NDA conference held March 31, 1998 with the Division, plans for a NDA filing for December 1998 were discussed and the following decisions were reached:

- ◆ No new studies were needed for the non-clinical, human pharmacokinetic and clinical programs. The Division agreed with the sponsor's proposal to cross-reference the ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® NDAs (NDAs 19-653 and 19-697, respectively) for the majority of nonclinical information on norgestimate and estradiol. Study ESTNRG-PHI-001 was deemed sufficient for multiple-dose pharmacokinetic information.
- ◆ The prevention of osteoporosis indication could be obtained by filing an ANDA with the Division of Generic Drug Products for the estradiol-only tablets (0.5, 1, and 2 mg strengths), and if approved, the claim could be applied to the cyclophasic regimen submitted in the NDA. The sponsor anticipated a July 1998 filing of the ANDA. Since the ANDA bioequivalence studies were conducted utilizing the 0.5 and 2 mg E<sub>2</sub> tablets, the 1mg E<sub>2</sub> dose must be shown to be proportional.
- ◆ The cyclophasic HRT regimen to be submitted is 1mg E<sub>2</sub>/1mg E<sub>2</sub> + 90  $\mu$ g NGM. The Division advised the sponsor they would have to provide convincing safety and efficacy data for the 1 mg E<sub>2</sub> dose regimen submitted for osteoporosis since the lowest effective dose of E<sub>2</sub> currently approved for osteoporosis is 0.5 mg.
- ◆ Stability data needed to be filed within 6 months of the original filing.
- ◆ The primary analysis should be absolute change from baseline and the intent-to-treat analysis is the primary analysis variable.

In subsequent post-meeting communications it was agreed that the sponsor could combine the study reports for the two pivotal cyclophasic HRT studies (ESTNRG-CHRT-102 and 103) into one report.

A pre-NDA teleconference, conducted with the sponsor on November 19, 1998, reached the following decisions:

- ◆ The Division will accept a 505(b)(2) NDA for osteoporosis if the bioequivalence is proven. The osteoporosis indication will be reviewed in this Division unless the sponsor asserts that the 1 mg E<sub>2</sub> dose is the lowest effective dose for the prevention of osteoporosis (the lowest effective dose of Estrace® for the prevention of osteoporosis is 0.5 mg).
- ◆ There are no patent issues regarding Estrace® (17 $\beta$ -estradiol).
- ◆ The labeling must be clear that the 1mg E<sub>2</sub>/1mg E<sub>2</sub> + 90  $\mu$ g NGM cyclophasic dosage regimen is for relief of vasomotor symptoms and protection of the endometrium in postmenopausal women with uteri who may benefit from osteoporosis prevention. A Phase IV study may be needed to determine the lowest effective dose of this regimen.

ESTNRG-CHRT-102 was a 18 center, double-blind, parallel group, dose-ranging study in which 352 healthy postmenopausal women with intact uteri, aged 40-65 years, were randomized to receive one year (twelve 30-day cycles) of one of the following treatment regimens: continuous daily 1 mg E<sub>2</sub> alone, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM utilizing a continuous repeating schedule of 3-days of E<sub>2</sub> alone followed by 3 days of E<sub>2</sub> + NGM, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM, continuous daily 2 mg E<sub>2</sub> alone, 2 mg E<sub>2</sub>/2 mg E<sub>2</sub> + 90 µg NGM, and 2 mg E<sub>2</sub>/2 mg E<sub>2</sub> + 180 µg NGM. By Protocol Amendment dated July 22, 1996, the groups receiving 2 mg E<sub>2</sub> regimens were discontinued. Endometrial biopsies were evaluated at screening and end-of-study as the primary efficacy variable. Secondary efficacy evaluations included vaginal bleeding, vasomotor symptoms, and vaginal epithelial cytology.

ESTNRG-CHRT-103 was a 67 center, double-blind, parallel group, dose-ranging study in which 1543 healthy postmenopausal women with intact uteri, aged 40-65 years, were randomized to receive the same doses as listed in Study 102 over a twelve month period following the same 3-days-on 3-days-off treatment schedule. By a Protocol Amendment dated September 5, 1996, the groups receiving 2 mg E<sub>2</sub> regimens were discontinued. Endometrial biopsies were evaluated at screening and end-of-study (Cycle 12) as the primary efficacy variable. Vasomotor symptoms were evaluated as a secondary efficacy variable.

ESTNRG-CHRT-104 was a 22 center, double-blind, parallel group study in which 106 women, with and without uteri, who had moderate to severe vasomotor symptoms and vulvovaginal atrophy after surgically induced or natural menopause, aged 29 to 66 years, were randomized to receive either 1 mg E<sub>2</sub>, 2 mg E<sub>2</sub>, or placebo for a twelve week period. The frequency and severity of daily hot flushes and vaginal epithelial cytology were evaluated. Transvaginal ultrasonography and endometrial biopsies were performed for women with intact uteri. By Protocol Amendment dated November 5, 1996 the enrollment of these 106 women was discontinued and a second randomization was initiated involving 145 women (excluding the previously enrolled 106 women), aged 28 to 63. Women in this second randomization group were randomized to receive either 0.5 mg E<sub>2</sub>, 1 mg E<sub>2</sub>, or placebo.

In this submission, Study N93-072, conducted in the US and Costa Rica, provides additional supportive data for vasomotor symptoms, vulvovaginal atrophy and prevention of endometrial hyperplasia. Study CC2636-C-101 (conducted in Finland, Sweden, Belgium, and The Netherlands) and ESTNRG-CHRT-105, an extension of C-101, provides additional supportive data for the prevention of endometrial hyperplasia and vasomotor symptoms.

The tradename "PERFEST" was submitted to the IND. Following comments from the Division, the sponsor revised the tradename and proposed "PREFEST" for consideration by the Labeling and Nomenclature Committee. On June 23, 1998, the Labeling and Nomenclature Committee advised the sponsor that the proposed tradename was acceptable.

## 2. Background

### 2.1 Regulatory history

Please see the Resume section above for a description of activity under IND \_\_\_\_\_ and the results of pre-NDA conferences with the sponsor. The clinical development program for Ortho-Prefest™ consisted of seven completed Phase 1 studies in 241 postmenopausal women and six completed Phase 2 and 3 safety and efficacy studies in 3,184 postmenopausal women.

The NDA drug product, Ortho-Prefest™ Tablets is not marketed in any country worldwide.

### 2.2 Clinical implications of preclinical sections

#### 2.2.1 Chemistry, manufacturing and controls

Please refer to Chemistry, Manufacturing and Controls Review.

The active compounds included in this application are 17 $\beta$ -estradiol, USP (micronized) and norgestimate (micronized). 17 $\beta$ -estradiol, USP is synthesized by Norgestimate is synthesized by

Each tablet for oral administration contains 1.0 mg estradiol alone or 1.0 mg estradiol and 0.09 mg of norgestimate, and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, magnesium stearate, and lactose monohydrate.

### 2.2.2 Pharmacology and toxicology

Please refer to Pharmacology Review.

The use of estrogens in hormone replacement therapy is well established, and estradiol has been approved for the treatment of moderate-to-severe vasomotor symptoms, vulvar and vaginal atrophy, and the prevention of osteoporosis. The interaction of estrogens with specific receptors in hormone-sensitive tissues leads to expression of the biologic effects of these compounds. Estradiol has a confirmed high affinity for the estrogen receptor.

Norgestimate (NGM) is an active progestin and binds to progestational receptor in vitro. Nonclinical studies demonstrate that norgestimate is minimally androgenic.

No studies have examined the toxicity of NGM in combination with estradiol. However, NGM alone and in combination with ethinyl estradiol has been extensively evaluated in preclinical toxicity studies at higher doses without unexpected adverse events (NDA 21-040, Volume 3, page 146).

### 2.3 Human pharmacokinetics/bioavailability

Please refer to the Clinical Pharmacology and Biopharmaceutics Review.

In humans, all estrogens, conjugated and unconjugated, are found in circulation either physiologically free or specifically bound with high affinity to the sex hormone-binding globulin (SHBG). 17d-NGM, NGM's major metabolite, binds primarily to serum proteins.

All estradiol tablets were formulated using a dry blend of micronized estradiol. The E<sub>2</sub>/NGM tablets of the CYCLOPHASIC HRT regimen were first formulated using the same formulation matrix as in the two oral contraceptive products, ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® (termed the "wet-manufacturing process" formulation). Later, a new modified formulation, the "dry-manufacturing process" formulation was established. Both wet- and dry-manufacturing process tablets were used in the clinical studies. The sponsor used the dry-manufacturing process tablets in pivotal Studies ESTNRG-CHRT-102, 103, and 104. The wet-manufacturing process tablets were used in the three supportive studies (N93-072, Study CC2636-C-101, and ESTNRG-CHRT-105).

Results of Study ESTNRG-PHI-008 showed that the dry- and wet-manufacturing process tablets were bioequivalent in estrone, estrone sulfate and norgestimate; i.e., equivalent systemic exposure (as indicated by AUC) and the equivalent rate of absorption (as indicated by C<sub>max</sub> and T<sub>max</sub>) were observed. For E<sub>2</sub> and 17d-NGM, the two formulations were equivalent in systemic exposure but not in the rate of absorption (the wet-manufacturing process tablet reached its C<sub>max</sub> faster and higher than the dry-manufacturing process tablet). The drug product intended for marketing is formulated according to the dry-manufacturing process.

The effect of food and the single-dose and multiple-dose pharmacokinetics of estradiol, NGM, and their metabolites were evaluated in Study ESTNRG-PHI-004 and -001, respectively. Study results show that a high-fat meal does not affect the AUC of estradiol, estrone, estrone sulfate, and 17d-

NGM; does not affect the  $C_{max}$  of estradiol, but decreases the  $C_{max}$  for 17 $\beta$ -NGM by 16%. 17 $\beta$ -estradiol reaches its  $C_{max}$  at approximately 7 hours in postmenopausal women receiving CYCLOPHASIC HRT. 17D-NGM reaches  $C_{max}$  at approximately 2 hours after single-dose.

It has been demonstrated the 17 $\beta$ -NGM gradually declines to the assay detection limit (110 pg/ml) at 24 hours after the last  $E_2$ /NGM dose and continues to decline to nearly zero by the end of the three days of estradiol-only therapy, indicating that exposure to NGM is intermittent.

### 3. Description of clinical data source

The clinical development program for CYCLOPHASIC HRT consisted of seven completed Phase I studies with 241 postmenopausal women and six completed Phase II and III safety and efficacy studies with 3,184 postmenopausal women.

Five CYCLOPHASIC HRT regimens were studied including three regimens containing 1 mg estradiol plus 1 mg estradiol in combination with 30, 90, or 180  $\mu$ g of NGM; and two regimens containing 2 mg estradiol plus 2 mg estradiol in combination with 90 and 180  $\mu$ g of NGM. Analysis of data from the pivotal Phase III clinical studies resulted in the final selection of the regimen containing 1mg estradiol plus 1 mg estradiol in combination with 90  $\mu$ g NGM as the dose proposed for marketing. This regimen has been assigned the tradename ORTHO-PREFEST™.

Pivotal Studies ESTNRG-CHRT-102/103 (cyclophasic regimens), and ESTNRG-CHRT -104 (estradiol alone) provide data supporting the treatment of vasomotor symptoms, vulvovaginal atrophy, and the prevention of endometrial hyperplasia. Studies N93-072, CC2636-C-101, and ESTNRG-CHRT-105 provide supportive data. The primary safety data are based on the 2,908 evaluable subjects from the five Phase II and III combination regimen studies. Supportive safety results are provided by Study 104, as well as the seven completed Phase I studies and two ongoing blinded Phase II/III studies. Study 104 was the only study that included the 0.5 mg dose of estradiol, all other studies included only 1 and 2 mg estradiol doses.

When the results of the interim analysis, performed in May 1996, of bleeding from Study N93-072 revealed unfavorable bleeding results for the 2 mg estradiol regimens in the Phase III trials, the sponsor made a decision to discontinue currently-enrolled subjects receiving these regimens from those studies and to discontinue enrollment into these treatment groups.

Included with this NDA is a FDA 505(b)(2) filing for an osteoporosis indication based on the results of bioequivalence studies ESTNRG-PHI-006 and -007 comparing estradiol formulations to be marketed with Estrace® (estradiol tablets) approved for the prevention of osteoporosis. During a teleconference with the sponsor on November 19, 1998, the Division indicated that the 505(b)(2) application would be an appropriate method for gaining approval of the osteoporosis prevention claim if bioequivalence is proven.

### 4. Clinical trial ESTNRG-CHRT-104

#### 4.1 Objectives/rationale

The primary source of estrogen in normally cycling women is the ovarian follicle which secretes 70 to 500 micrograms of 17 $\beta$ -estradiol daily (the principle estrogen produced by the functioning premenopausal ovary) depending on the phase of the menstrual cycle. The second major naturally occurring human estrogen is estrone. At menopause, no further ovulatory cycles are produced and the production of 17 $\beta$ -estradiol decreases dramatically. After menopause, most endogenous estrogen is produced by the conversion of androstenedione, secreted by the adrenal cortex, to estrone by adipose tissues. In postmenopausal women, estrone sulfate is the most abundant circulating estrogen.

Administered estrogens and their sulfate esters are handled within the body essentially the same as endogenous estrogens. Estrogens are metabolized and conjugated by the liver in order to increase their

solubility in water in preparation for excretion. Naturally occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin. Only unbound estrogens enter target cells. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Common symptoms of the menopause and postmenopause years include hot flushes, paresthesias, palpitations, cold hands and feet, headaches, vertigo, irritability, anxiety, nervousness, depression, fatigue, weight gain, insomnia, night sweats, forgetfulness, and inability to concentrate. Hot flushes, certainly the most distinctive and distressing among the various neuroendocrine manifestations of the menopause, are experienced by more than 75% of women with decreasing estrogen levels (and as high as 94-100% of oophorectomized women), and may persist for one or more years. Many women will have mild (or no) menopausal symptoms and will not need to use estrogen drugs for these symptoms. Others may need to take estrogens temporarily while their bodies adjust to lower estrogen levels. The majority of women who require estrogen replacement therapy for the relief of vasomotor symptoms will not need it for longer than a six month treatment duration.

Study ESTNRG-CHRT-104 was designed to be an adequate and well-controlled study to evaluate the safety and efficacy of two oral doses of  $E_2$  alone for the relief of moderate-to-severe vasomotor symptoms and the treatment of vulvovaginal atrophy.

#### 4.2 Design

Study ESTNRG-CHRT-104 was a 22 center, double-blind, placebo-controlled study conducted in the US in which a total of 251 subjects (naturally menopausal aged 40-60 years, or surgically menopausal aged 26-60 years) were randomized to receive placebo, 1mg, and 2 mg of  $E_2$  (Randomization 1 = 106 subjects) or placebo, 0.5 mg, and 1 mg of  $E_2$  (Randomization 2 = 145 subjects) for 12 weeks.

Initially, the two doses of  $E_2$  under study were 1 and 2 mg. However, an interim analysis of Phase II, Study N93-072 revealed high rates of vaginal bleeding/spotting with the 2 mg regimens, and a decision was reached to discontinue evaluation of the 2 mg dose. An amendment to this protocol, dated 11/5/96, replaced the 2 mg estradiol dose with 0.5 mg of estradiol. No additional subjects were thereafter randomized to the 2 mg treatment arm. For the purpose of this review, no efficacy data is included for subjects receiving 2 mg of  $E_2$  in Randomization 1.

Following the exclusion of the 2 mg treatment arm, the primary objective of this study was to evaluate the safety and efficacy of the 0.5 mg and 1 mg estradiol doses, compared to placebo, for the relief of moderate-to-severe vasomotor symptoms. The secondary study objective was to evaluate the efficacy of the two  $E_2$  doses for the treatment of vulvovaginal atrophy utilizing the maturation index.

#### 4.3 Study population

There were 106 subjects in Randomization 1 (2 mg  $E_2$ =35, 1 mg  $E_2$ =33, placebo=38) with a mean age of 48.8 years (SD=6.85). Ninety-two percent (n=97) were Caucasian, 66% (n=70) had prior HRT use and the median months since last menses ranges from 82.6 to 93.2 (see Table 1). Two subjects in Randomization 1 (one each in the 1 mg estradiol group and the placebo group) were enrolled but given no medication.

Among the 145 subjects in Randomization 2 (1 mg  $E_2$ =48, 0.5 mg  $E_2$ =48, placebo=49) the mean age was 48.4 (SD=6.77). 83% (n=120) were Caucasian, 50% (n=72) had prior HRT use and the median months since last menses ranged from 64.9 to 75.2 (see Table 2). Three subjects in this group (2 in the 0.5 mg estradiol group and 1 in the placebo group) were enrolled but given no medication.

Table 1: Demographics of Patient Population by Treatment – Randomization 1

Characteristics	Continuous 2 mg E <sub>2</sub> (N=35)		Continuous 1 mg E <sub>2</sub> (N=33)		Placebo (N=38)		Total (N=106)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	47.2	(5.88)	48.8	(6.54)	50.3	(7.73)	48.8	(6.85)
Height (cm)	165.1	(7.90)	164.0	(8.36)	163.8	(5.99)	164.3	(7.38)
Weight (kg)	73.9	(13.1)	72.9	(11.8)	69.9	(12.7)	72.2	(12.6)
Body Mass Index	27.2	(4.71)	27.1	(3.67)	26.0	(3.98)	26.7	(4.15)
Median months since last menses	91.5		82.6		93.2		86.3	
Hysterectomy								
No	10 (29%)		12 (36%)		8 (21%)		30 (28%)	
Yes	25 (71%)		21 (64%)		30 (79%)		76 (72%)	
Prior HRT								
No	12 (34%)		15 (45%)		9 (24%)		36 (34%)	
Yes	23 (66%)		18 (55%)		29 (76%)		70 (66%)	
Race								
White	31 (89%)		30 (91%)		36 (95%)		97 (92%)	
Black	3 (9%)		2 (6%)		2 (5%)		7 (7%)	
Other	1 (3%)		1 (3%)		0 (0%)		2 (2%)	
Smoker (%)	10 (29%)		10 (30%)		9 (24%)		29 (27%)	

Source: NDA 21-040, Item 8, Volume 15, page 42

Table 2: Demographics of Patient Population by Treatment – Randomization 2

Characteristics	Continuous 1 mg E <sub>2</sub> (N=48)		Continuous 0.5 mg E <sub>2</sub> (N=48)		Placebo (N=49)		Total (n=145)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	48.7	(6.09)	48.4	(6.63)	48.1	(7.60)	48.4	(6.77)
Height (cm)	163.7	(7.32)	164.2	(5.54)	164.5	(7.41)	164.1	(6.78)
Weight (kg)	72.5	(16.1)	71.6	(12.3)	70.4	(10.9)	71.5	(13.2)
Body Mass Index	26.9	(4.49)	26.5	(4.41)	26.1	(4.00)	26.5	(4.29)
Median months since last menses	75.2		64.9		73.2		71.3	
Hysterectomy								
No	15 (31%)		17 (38%)		11 (22%)		44 (30%)	
Yes	33 (69%)		30 (63%)		38 (78%)		101 (70%)	
Prior HRT								
No	26 (54%)		24 (50%)		23 (47%)		73 (50%)	
Yes	22 (46%)		24 (50%)		26 (53%)		72 (50%)	
Race								
White	41 (85%)		40 (83%)		39 (80%)		120 (83%)	
Black	2 (4%)		6 (13%)		4 (8%)		12 (8%)	
Asian	2 (4%)		0 (0%)		1 (2%)		3 (2%)	
Other	3 (6%)		2 (4%)		5 (10%)		10 (7%)	
Smoker (%)	20 (42%)		16 (33%)		19 (39%)		55 (38%)	

Source: NDA 21-040, Item 8, Volume 15, page 43

#### 4.4 Inclusion and exclusion criteria

Inclusion criteria (NDA 21-040, Item 8, Volume 15, page 24-25)

- Absence of spontaneous vaginal bleeding for at least 12 months, with or without uteri (natural menopause), 40-60 years of age;
- Three weeks post-surgical bilateral oophorectomy with or without a hysterectomy (surgically menopausal), 26-60 years of age;
- Serum FSH levels  $\geq 40$  mIU/ml in subjects with prior hormone replacement therapy;
- Serum FSH levels  $\geq 30$  mIU/ml in subjects without prior HRT use but with amenorrhea for at least 12 months or surgically menopausal for at least three weeks;
- Serum estradiol levels  $\leq 20$  pg/ml;
- Average of 8 or more moderate or severe hot flushes per day during a period of 14 full consecutive days prior to randomization;
- All hormone replacement therapy discontinued eight weeks prior to the randomization visit; no exposure to injectable or implantable sex steroids within six months of admission;
- Body weight within the  $\pm 35\%$  range of body mass index;
- Good overall health as evidence by medical history, ECG, physical examination, laboratory profiles, mammogram, breast exam and Pap smear;
- Highly motivated and signed an informed consent document.

Exclusion criteria (NDA 21-040, Item 8, Volume 15, pages 25-27)

- History or presence of endometrial hyperplasia or carcinoma, known or suspected cancer of the breast, estrogen-dependent neoplasia or other neoplasia (exception of non-recurring basal cell carcinoma of the skin);
- Known or suspected pregnancy;
- Undiagnosed abnormal vaginal bleeding;
- History of or active thrombophlebitis, thrombosis, or thromboembolic disorders;
- History of cerebral vascular disease, coronary artery disease, myocardial infarction, or uncontrolled hypertension;
- Benign or malignant liver disease, gallbladder disease which developed during the use of oral contraceptives or other estrogen-containing products, increased frequency or severity of migraines during previous estrogen therapy;
- Endocrine disease other than controlled thyroid disease;
- Use of the following medications within two weeks of screening: dopaminergic or antidopaminergic drugs, clonidine, digitalis preparations, psychotropic medication, narcotic analgesics, or  $> 14$  days of antihistamines;
- History or presence of chronic alcoholism, drug addiction or severe depression;
- Clinically significant abnormal screening laboratory values;
- Smoking more than 10 cigarettes a day;
- An acute systemic infection within 7 days prior to admission;
- Hypersensitivity or allergy to study drug ingredients;
- Concurrent participation in another clinical trial or receiving an experimental drug or device in the 30 days prior to study admission.

#### 4.5 Screening period

At least 14 days prior to randomization, subjects recorded daily number of hot flushes and night sweats and the severity of each as mild, moderate, or severe (see NDA 21-040, Item 8, Volume 15, page 32 for a full description of mild, moderate, and severe). The presence or absence of vaginal dryness was also recorded daily.

#### 4.6 Baseline period

A physical examination (with vital signs and weight) and gynecologic examination (including breast and pelvic examinations, Pap smear, and a maturation index) were performed. Laboratory evaluations including hematology (hemoglobin, hematocrit, RBC, WBC with differential, and platelets), serum

chemistry (total bilirubin, alkaline phosphatase, LDH, ALT, AST, BUN, creatinine, uric acid, phosphorus, glucose, calcium, sodium, potassium, chloride, bicarbonate, total protein, albumin, cholesterol, and triglycerides), and urinalysis were analyzed. All Pap smears were sent to the central pathology laboratory (Kyto Diagnostics) for analysis. A mammogram was performed if no written negative result was available within 6 months of Visit 1. Every subject with a uterus underwent a transvaginal ultrasound, and if the endometrial thickness was > 5 mm an endometrial biopsy was performed. Both were repeated at the end of the treatment phase in each subject with a uterus.

#### 4.7 Treatment period

All study drug tablets were identical in appearance and were packaged in identically appearing blister drug cards. Subjects were instructed to take one tablet by mouth daily at bedtime, preferably between 9 p.m. and 12 midnight. Subjects recorded tablet-taking daily on diary cards. Each subject with a uterus recorded vaginal bleeding/spotting daily during the treatment period.

Following randomization (Visit 2, Study Day 1), subjects returned to the study site for four additional treatment visits (Visit 3, Study Days 8-14; Visit 4, Study Days 22-28; Visit 5, Study Days 50-56, and Visit 6, Study Days 78-84). At Visit 6 or early termination (if one month since Visit 1), a physical and gynecologic examination, Pap smear, vital signs and laboratory profile were performed. At early termination, a maturation index was performed if the subject had completed at least 8 weeks of treatment.

#### 4.8 Evaluation period

During the pretreatment period (at least 14 days prior to randomization) and throughout the double-blind treatment period, subjects recorded daily number of hot flushes and night sweats and the severity of each episode (mild, moderate, and severe). The presence or absence of vaginal dryness was recorded daily.

From data collected and recorded by the patient, the primary efficacy criterion, the mean number of moderate-to-severe hot flushes per day was summarized per treatment group at baseline (recorded in the 7 days prior to randomization) and for each week of the 12-week trial. The secondary efficacy criterion was to evaluate treatment of vulvovaginal atrophy utilizing the maturation index (an increase in the percentage of intermediate or superficial cells and a decrease in the percentage of parabasal cells).

#### 4.9 Withdrawals and compliance

As shown in Table 3, the overall completion rate was 88% (93 of 106 subjects) in Randomization 1 and 84% (122 of 145 subjects) in Randomization 2. In Randomization 1, the completion rate was similar for the 1 and 2 mg estradiol groups (94% and 97%), but lower for the placebo group (74%). All three groups had similar completion rates in Randomization 2 (82% to 88%).

Thirteen subjects (12%) withdrew from Randomization 1. One subject (3%) in the 2 mg E<sub>2</sub> group and 5 subjects (13%) in the placebo group withdrew because of adverse events (including one each = MVA, urticaria, leg cramps, headache/sinusitis, and two subjects with mood swings). The only reasons for withdrawal in the 1 mg E<sub>2</sub> group (1 subject each) were "subject choice" and "lost to follow-up". Adverse events (n=5[13%]) were the most common reason for withdrawal in the placebo group.

Twenty-three subjects (16%) withdrew from Randomization 2. "Lost to follow-up" was the most frequent reason for withdrawal in the 0.5 mg E<sub>2</sub> group and the placebo group (both n=4[8%]), while "subject choice" was most frequent in the 1 mg E<sub>2</sub> group (n=3[6%]). Under "Other" in Table 3, one subject (2%) in the 0.5 mg E<sub>2</sub> group was withdrawn for non-compliance and two subjects (4%) in the placebo group were withdrawn because they experienced no relief of vasomotor symptoms. Two subjects in the 1 mg E<sub>2</sub> group (4%) and two subjects in the placebo group (4%) withdrew because of

adverse events (including one each = migraine, dyspepsia, and alopecia, and one lung cancer in the placebo group).

Table 3: Enrollment, Completion, and Withdrawal Information

Randomization 1								
	2 mg E <sub>2</sub>		1 mg E <sub>2</sub>		Placebo		Total	
	N	(%) <sup>a</sup>	N	(%)	N	(%)	N	(%)
No. Randomized	35		33		38		106	
No. Completed	34	(97%)	31	(94%)	28	(74%)	93	(88%)
Withdrawn	1	(3%)	2	(6%)	10	(26%)	13	(12%)
Adverse Event	1	(3%)	0	(0%)	5	(13%)	6	(6%)
Lost to follow-up	0	(0%)	1	(3%)	1	(3%)	2	(2%)
Subject choice	0	(0%)	1	(3%)	3	(8%)	4	(4%)
Other	0	(0%)	0	(0%)	1	(3%)	1	(1%)
Randomization 2								
	1 mg E <sub>2</sub>		0.5 mg E <sub>2</sub>		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
No. Randomized	48		48		49		145	
No. Completed	42	(88%)	40	(83%)	40	(82%)	122	(84%)
Withdrawn	6	(13%)	8	(17%)	9	(18%)	23	(16%)
Adverse event	2	(4%)	0	(0%)	2	(4%)	4	(3%)
Lost to follow-up	1	(2%)	4	(8%)	4	(8%)	9	(6%)
Subject choice	3	(6%)	3	(6%)	1	(2%)	7	(5%)
Other	0	(0%)	1	(2%)	2	(4%)	3	(2%)

<sup>a</sup> Percentage of the number of subjects enrolled (randomized to treatment) in the group.

Source: NDA 21-040, Item 8, Volume 15, Table 3, page 45

#### 4.10 Protocol deviations

Two subjects in Randomization 1 and one subject in Randomization 2 were older than 60 years of age, the maximum age specified in the protocol inclusion criteria.

Four subjects in Randomization 1 were enrolled with baseline estradiol and FSH values outside the inclusion limits (3 subjects had E<sub>2</sub> values higher than 20 pg/ml, 1 subject had a FSH value lower than 40mIU/ml). In Randomization 2, four subjects had baseline E<sub>2</sub> values higher than 20 pg/ml and 6 subjects had FSH values lower than 40mIU/ml.

Nine subjects in Randomization 1 and 18 subjects in Randomization 2 took more than 28 tablets between the week 8 visit and the final visit (range 29-38 tablets for Randomization 1; 29-63 tablets in Randomization 2).

#### 4.11 Efficacy analysis

The primary objective of this study was to evaluate the efficacy of estradiol in relieving moderate-to-severe vasomotor symptoms. The mean number of hot flashes per day was summarized per treatment group at baseline (last seven days of the pretreatment phase) and for each week of the treatment period. The secondary objective was to evaluate treatment of vulvovaginal atrophy utilizing the maturation index. An increase in the percentage of intermediate or superficial cells and a decrease in the percentage of parabasal cells reflect an estrogen effect.

It was assumed that the placebo group could have up to 30% decrease in the number of hot flashes and that the active treatment group could have a 65% or greater decrease, and that the standard deviation would be 48%. Anticipating an overall dropout rate of 35%, the recommended sample size was 50 subjects per study arm.

Because evaluation of the Ortho-Prefest™ regimens using 2 mg had been discontinued, the efficacy results for Randomization 1 are only cross-referenced as appropriate.

The difference between the 1 mg E<sub>2</sub> group and the placebo group in Randomization 2, for the mean number of moderate to severe hot flushes per week, was statistically significant at Week 4 (p < 0.001) and sustained through Week 12 (p < 0.001). The difference between the 0.5 mg E<sub>2</sub> group and the placebo group, for the mean number of moderate-to-severe hot flushes per week, was statistically significant beginning at Week 8 (p=0.006) and sustained through Week 12 (p=0.006). See Table 4.

Table 4: Change in the Mean Number of Moderate-to-Severe Hot Flushes during Therapy in all Subjects with ≥ 7 Moderate-to-Severe Hot Flushes at Baseline, Study 104

Week	0.5 mg E <sub>2</sub> N=47	1 mg E <sub>2</sub> N=48	Placebo N=48
Baseline			
Mean #	13.02	14.56	13.16
Week 4			
Mean #	5.68	3.34	6.13
Mean Change	-7.46	-11.49	-6.51
Week 8			
Mean #	3.42	2.33	5.59
Mean Change	-8.85	-12.70	-6.83
Week 12			
Mean #	3.46	1.55	5.90
Mean Change	-8.90	-13.65	-6.60

Source: Adapted from information provided by the sponsor on June 11, 1999 and August 6, 1999 following a Division request for information.

The maturation index results for Randomization 2 showed that both the 0.5 mg and the 1 mg E<sub>2</sub> treatment groups had decreases in the number of parabasal cells and increases in the number of superficial cells. On the other hand, the placebo group showed an increase in parabasal cells but also showed an increase in superficial cells. See Table 5.

Table 5: Subjects with Maturation Index Results – Randomization 2

	Baseline Mean ± SE	End-of-Treatment Mean ± SE <sup>a</sup>	Mean Change ± SE
<b>Continuous 1 mg E<sub>2</sub> (n=34<sup>b</sup>)</b>			
Parabasal Cells (%)	8.8 ± 4.42	0.0 ± 0.0	-8.8 ± 4.42
Intermediate Cells (%)	83.4 ± 4.74	78.5 ± 4.67	-4.9 ± 5.95
Superficial Cells (%)	7.8 ± 2.66	21.5 ± 4.67	13.7 ± 4.88
<b>Continuous 0.5 mg E<sub>2</sub> (n=33<sup>b</sup>)</b>			
Parabasal Cells (%)	13.0 ± 4.78	0.3 ± 0.30	-13.0 ± 4.71
Intermediate Cells (%)	76.7 ± 5.32	80.8 ± 3.46	4.1 ± 5.90
Superficial Cells (%)	10.3 ± 3.65	18.9 ± 3.47	8.6 ± 4.38
<b>Placebo (n=30<sup>b</sup>)</b>			
Parabasal Cells (%)	8.7 ± 4.44	15.2 ± 6.23	6.5 ± 3.91
Intermediate Cells (%)	86.7 ± 4.56	74.7 ± 6.45	-12.0 ± 4.35
Superficial Cells (%)	4.7 ± 1.96	10.2 ± 3.66	5.5 ± 3.28

<sup>a</sup> Vaginal smears were obtained between 3 weeks prior to the end of treatment and 5 days after withdrawal from the study

<sup>b</sup> Number of subjects with maturation indices at both the start and the end of treatment, and with at least 8 weeks in the study

Source: NDA 21-040, Item 8, Volume 15, Table 7, page 54

Table 6 summarizes the analysis of the shift from parabasal cells to superficial cells at the end of treatment. The shift was calculated for each subject by subtracting the difference between the percent of superficial and parabasal cells at baseline from the difference at the end of treatment. In both the 0.5

and 1 mg treatment groups there was a "shift to the right" with an increase in superficial cells and a decrease in parabasal cells. The difference from placebo, which essentially showed a "shift to the left" with a greater increase in parabasal cells than the reported increase in superficial cells, is statistically significant ( $p=0.001$  for 1 mg and  $p=0.004$  for 0.5 mg  $E_2$ ).

Table 6: Shift from Parabasal to Superficial Cells – Randomization 2

Treatment Group	N	Mean	Median	p-Value <sup>a</sup>
Continuous 1 mg $E_2$	34	22.5	10	0.001
Continuous 0.5 mg $E_2$	33	21.4	10	0.004
Placebo	30	-1.0	0	---

<sup>a</sup> Difference from placebo, based on ANOVA with treatment and center as factors.  
Source: NDA 21-040, Item 8, Volume 15, Table 8, page 54

The proportion of subjects without reported vaginal dryness increased during the course of treatment for all three groups in Randomization 2. The largest change occurred with the 1 mg  $E_2$  dose. At baseline, 68.5% of 48 subjects randomized into the 1 mg  $E_2$  treatment group reported no vaginal dryness. By the end of 12 weeks of treatment 86% of 42 subjects reported no vaginal dryness. However, the placebo group reported a larger change in absence of vaginal dryness than the 0.5 mg  $E_2$  treatment group (60.5% to 73.8% and 68.5% to 76.1%, respectively).

#### Reviewer's comments

It should be noted that this study protocol did not incorporate inclusion criteria for atrophic vaginitis. There were no pretreatment or post-treatment assessments of associated dyspareunia, dysuria, post-coital bleeding, urinary urgency, or vaginal burning, and no pretreatment or post-treatment investigator assessment of vaginal color, pH, or the presence or absence of petechiae, friability and/or dryness. For vaginal dryness, study participants only recorded a yes or no response in the daily diary. The study participant was not asked to indicate the severity of vaginal dryness experienced.

However, maturation values assessed during the study remained significantly improved over baseline ( $p=0.001$  for the 1 mg  $E_2$  group). There was a reported improvement in vaginal dryness, but no correlation can be made between the parabasal cell results and the subject's evaluation of vaginal dryness.

#### 4.12 Safety analysis

There were no deaths during this study.

Seventy-seven percent ( $n=80$ ) of subjects in Randomization 1 reported 339 adverse event occurrences. The 2 mg  $E_2$  group had the largest number of subjects reporting adverse events (83% compared to 69% in the 1 mg group and 77% in the placebo group). Across the three treatment groups in Randomization 1, the most common adverse events reported (excluding endometrial hyperplasia) were upper respiratory tract infection ( $n=17$ [16.3%]), headache ( $n=14$ [13.4%]), and vaginitis ( $n=8$ [8%]).

Seventy percent ( $n=100$ ) of subjects in Randomization 2 reported 475 adverse event occurrences. The 0.5 mg  $E_2$  group had the largest number of subjects reporting adverse events (74% compared to 67% in the 2 mg group and 71% in the placebo group). Excluding endometrial hyperplasia, the most common adverse events reported across the three treatment groups in Randomization 2 were headache ( $n=17$ [11.9%]), upper respiratory tract infection ( $n=14$ [9.8%]), and abdominal pain ( $n=11$ [7.7%]).

Six subjects in Randomization 1 and four subjects in Randomization 2 discontinued due to an adverse event. Seven of these subjects were in the placebo group, one was in the 2 mg group, and two were in the 1 mg  $E_2$  treatment group.

Summaries of treatment-emergent events that occurred with a frequency of  $\geq 5\%$  by preferred term and treatment group in Randomization 1 and 2 (excluding endometrial hyperplasia) are presented in Table 7. The adverse events reported by the greatest percentage of subjects across treatment groups in Randomization 1 were upper respiratory tract infection (n=17 of 104 [16.3%]), headache (n=14 of 104 [13.4%]), and vaginitis (n=8 of 104 [7.6%]). In Randomization 2, the adverse events reported by the greatest percentage of subjects across treatment groups were headache (17 of 142 [11.9%]), upper respiratory tract infection (17 of 142 [9.8%]), and abdominal pain (11 of 142 [7.7%]).

Table 7: Adverse Events Reported with an Incidence of  $\geq 5\%$  in Any Treatment Group, Randomization 1 and 2, Study 104

Adverse Event <sup>b</sup> (by Preferred Term)	Randomization 1			Randomization 2 <sup>a</sup>		
	2 mg E <sub>2</sub> N=35 N (%)	1 mg E <sub>2</sub> N=32 N (%)	Placebo N=37 N (%)	1 mg E <sub>2</sub> N=48 N (%)	0.5 mg E <sub>2</sub> N=46 N (%)	Placebo N=48 N (%)
Upper respiratory tract infection	3 (9)	5 (16)	9 (24)	6 (13)	3 (7)	5 (10)
Headache	4 (11)	4 (13)	6 (16)	5 (10)	7 (15)	5 (10)
Abdominal pain	1 (3)	3 (9)	0 (0)	5 (10)	4 (9)	2 (4)
Breast pain	2 (6)	0 (0)	2 (5)	5 (10)	2 (4)	2 (4)
Nausea	1 (3)	2 (6)	1 (3)	5 (10)	2 (4)	1 (2)
Sinusitis	1 (3)	1 (3)	2 (5)	5 (10)	3 (7)	1 (2)
Vaginitis	5 (14)	1 (3)	2 (5)	5 (10)	0 (0)	4 (8)
Back pain	3 (9)	1 (3)	0 (0)	3 (6)	2 (4)	5 (10)
Injury	1 (3)	0 (0)	2 (5)	3 (6)	3 (7)	1 (2)
Leukorrhea	2 (6)	0 (0)	0 (0)	3 (6)	0 (0)	3 (6)
Diarrhea	0 (0)	0 (0)	2 (5)	2 (4)	3 (7)	2 (4)
Dyspepsia	3 (9)	0 (0)	0 (0)	2 (4)	3 (7)	3 (6)
Flatulence	0 (0)	0 (0)	0 (0)	2 (4)	3 (7)	1 (2)
Influenza-like symptoms	1 (3)	5 (16)	1 (3)	2 (4)	3 (7)	0 (0)
Myalgia	1 (3)	0 (0)	2 (5)	0 (0)	3 (7)	1 (2)
Cervical smear test positive	3 (9)	1 (3)	1 (3)	0 (0)	1 (2)	3 (6)
Dizziness	1 (3)	2 (6)	1 (3)	0 (0)	1 (2)	3 (6)
Arthralgia	1 (3)	1 (3)	5 (14)	0 (0)	0 (0)	0 (0)
Edema, generalized	1 (3)	2 (6)	1 (3)	0 (0)	0 (0)	0 (0)
Fatigue	2 (6)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)
Weight increase	2 (6)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)
Dysmenorrhea	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fracture, pathological	2 (6)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Insomnia	2 (6)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Urinary tract infection	2 (6)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Acne	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
Tooth ache	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)

<sup>a</sup> Adverse events are in the order of decreasing incidence within the 1 mg E<sub>2</sub> group.  
<sup>b</sup> Does not include endometrial hyperplasia, which is presented separately in Table 8.  
Source: NDA 21-040, Item 8, Volume 15, Tables 12a and 12b, pages 58-59.

Endometrial hyperplasia was the most significant adverse event occurring in both Randomization 1 and 2. Table 8, which combines all results in Study 104, shows that 30% of subjects (n=3 of 10 subjects with uteri) in the 2 mg E<sub>2</sub> group, 15% in the 1 mg group (n=4 of 27), 6% in the 0.5 mg group (n=1 of 18), and no subjects in the placebo group (n=0 of 19) developed endometrial hyperplasia.

Table 8: Incidence of Endometrial Hyperplasia as an Adverse Event in Randomization 1 and 2  
Number With Endometrial Hyperplasia/Number With Uterus (%)

Continuous 2 mg E <sub>2</sub>	Continuous 1 mg E <sub>2</sub>	Continuous 0.5 mg E <sub>2</sub>	Placebo
3/10 (30%)	4/27 (15%)	1/18 (6%)	0/19 (0%)

Source: Table 13, NDA 21-040, Item 8, Volume 15, page 59

Three cases of simple hyperplasia were diagnosed in the 2 mg E<sub>2</sub> treatment group. Of the four cases of hyperplasia diagnosed in the 1 mg E<sub>2</sub> treatment group, one was a simple hyperplasia, one a simple hyperplasia with focal necrosis, one a focal cystic hyperplasia, and one a complex hyperplasia. One case of simple hyperplasia was observed in the 0.5 mg E<sub>2</sub> group. All hyperplasia cases were treated with MPA or conjugated estrogens and MPA following biopsy diagnosis. The one patient in the 1 mg E<sub>2</sub> group, diagnosed with complex hyperplasia at end-of-study, and treated with four weeks of MPA was diagnosed with endometrial adenocarcinoma (Grade II with superficial invasion of the myometrium) on a repeat biopsy.

One placebo patient diagnosed with large-cell undifferentiated carcinoma of the right upper lobe of the lung with mediastinal spread to the right hilar and subcarinal lymph nodes was withdrawn from the study after taking 28 days of study drug.

#### Reviewer's comments

Adverse events reported during Study ESTNRG-CHRT-104 were generally similar to adverse events known to occur during treatment with estrogens. Among subjects with a uterus, endometrial hyperplasia was the only adverse event that showed meaningful differences between groups with 30% of the 2 mg E<sub>2</sub> dose developing hyperplasia. All seven of the reported endometrial hyperplasia and the one reported endometrial carcinoma (in the 1 mg E<sub>2</sub> treatment group) were considered to have a probable, likely, or certain relationship to estradiol.

#### 4.13 Summary of DSI audit

No DSI audits were completed under this protocol.

### 5. Clinical trial ESTNRG-CHRT-102 and ESTNRG-CHRT-103

#### 5.1 Objectives/rationale

Ortho-Prefest™ was the product used in these two clinical trials. Ortho-Prefest™ is a combination product that provides intermittent progestin treatment during continuous estradiol treatment. Three days of estradiol alone treatment is followed by three days of estradiol plus norgestimate treatment. This regimen (referred to in this review as cyclophasic) is repeated continuously.

This method of administration was first proposed by Upmalis and Casper in 1991 and is based on animal and human studies showing that progestin caused down-regulation of endometrial estrogen and progesterone receptors while estrogen up-regulates both type of receptors<sup>1,2</sup>. Therefore, receptor levels that decrease during the estrogen/progestin treatment would recover during the subsequent period of estrogen-only administration. Increases in the concentration of progestin receptors would allow the

<sup>1</sup> Upmalis DH, Jaffe ME, Casper RF. Receptor dynamics as applied to the delivery of sex steroids. Ann NY Acad Sci 1991;618:518-521.

<sup>2</sup> Casper RF. Regulation of estrogen/progestogen receptors in the endometrium. Int J Fertil 1996;41:16-21.

use of a lower dose of progestin to achieve the desired progestational effect on the endometrium exposed to continuous estrogen therapy<sup>3</sup>. The sponsor hypothesizes that giving progestin in a 3-days-on and 3-days-off schedule, with continuous estrogen, will minimize the amount of progestin required to protect the endometrium from developing hyperplasia.

Regimens investigated included 1 or 2 mg of estradiol in combination with 30, 90, and 180 µg of norgestimate with the E<sub>2</sub> administered continuously daily, and the NGM administered for three-day periods alternating with three-day periods free of NGM. As ESTNRG-CHRT-102 and 103 were of the same design with respect to the collection of data, the Division agreed, on August 8, 1995, that a combined report for Studies 102 and 103 could be submitted.

The primary objective of the combined Phase III studies was to evaluate the effects of the cyclophasic E<sub>2</sub>/NGM regimens on endometrial hyperplasia in postmenopausal women during one year of treatment. A separate objective in Study 102 was to evaluate the effects of cyclophasic E<sub>2</sub>/NGM regimens on blood lipids/lipoproteins, coagulation factors, carbohydrate metabolism, and serum SHBG concentrations.

Amendment 1 of each protocol was dated January 16, 1996. The changes were as follows:

- The entry requirements of a serum FSH concentration of  $\geq 40$  mIU/ml was modified for subjects who had not had previous HRT and whose last spontaneous menstrual period had occurred at least 12 months prior to the start of study: such subjects were allowed to have a serum FSH concentration of  $\geq 30$  mIU/ml for entry into the study.
- In the section on study procedures, it was clarified that the pretreatment period of recording the frequency and severity of hot flushes would be a minimum of 14 consecutive days immediately prior to the randomization visit (Visit 2), the visit at which study medication was dispensed.
- For endometrial biopsies (both prestudy and end of treatment), the requirement was added that for subjects with insufficient tissue for diagnosis, both the endometrial biopsy and the transvaginal ultrasonography had to be repeated if the endometrial thickness was greater than 5 mm. At prestudy, these additional procedures would allow the subject to enter the study, if otherwise eligible.

Amendment 2 (dated July 22, 1996 for Study 102 and dated September 5, 1996 for Study 103) included the following changes:

- Based on the interim analysis of bleeding from the Phase 2 study (Protocol N93-072), which showed that the 2 mg E<sub>2</sub> regimens were associated with relatively unfavorable patterns of bleeding, an amendment was made to each of the Phase 3 protocols specifying that the regimens containing 2 mg E<sub>2</sub> were to be discontinued from the studies. No additional subjects would be enrolled in these three treatment groups. A descriptive efficacy summary would be performed for these three treatment groups at the end of the study; the assessment of safety would not be altered. The blinding would not be broken before the end of the study.
- Enrolled subjects receiving the 2 mg E<sub>2</sub> dosage regimens would be discontinued at the next scheduled visit and have early termination procedures performed as specified in the Study Completion/Withdrawal section of the protocols.
- The clinical supplies department of RWJPRI would notify the investigators as to which subjects should be discontinued and which subject numbers should not be assigned to new subjects

## 5.2 Design

Each study was a multicenter (18 centers for Study 102 and 67 centers for Study 103), double-blind, parallel group, dose-ranging study in which 352 (Study 102, Amendment 2 reduced number to 200) and 1542 (Study 103, Amendment 2 reduced number to 1000) healthy postmenopausal women, aged

<sup>3</sup> Casper RF, MacLusky NJ, Vanin C, Brown TJ. Rationale for estrogen with interrupted progestin as a new low-dose hormonal replacement therapy. *J Soc Gynecol Invest* 1996;3:225-234.

40 to 65, who had experienced natural menopause at least 12 months prior to the start of the study, were randomized to receive one of the following seven treatment groups for 12 thirty-day cycles:

- Continuous 1 mg E<sub>2</sub>
- 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM
- 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM
- 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM
- Continuous 2 mg E<sub>2</sub>
- 2 mg E<sub>2</sub>/2 mg E<sub>2</sub> + 90 µg NGM
- 2 mg E<sub>2</sub>/2 mg E<sub>2</sub> + 180 µg NGM

Subjects were instructed to take one tablet of the assigned study medication by mouth daily at bedtime, preferably between 9 p.m. and 12 midnight, and maintain the same schedule throughout the study.

When an interim analysis of bleeding data obtained at six months of treatment in the on-going Phase II study (Study N93-072) revealed unfavorable results for vaginal bleeding in the treatment groups receiving the 2 mg E<sub>2</sub> regimens, both Studies 102/103 were amended to discontinue the three 2 mg E<sub>2</sub> dosage groups from these Phase III studies. The approximate numbers of subjects discontinued at this time were 80 in Study 102 and 300 in Study 103.

Following the exclusion of the 2 mg treatment arms, the primary objective of these studies were to evaluate the safety and efficacy of the remaining doses to protect the endometrium. All descriptions that appear in the forthcoming sections refer to those of the amended protocols.

### 5.3 Study population

There were 1253 subjects with treatment data (randomized subjects who took at least one tablet of study drug) in Studies ESTNRG-CHRT-102/103 who received one of the four 1mg E<sub>2</sub> treatment regimens with a mean age of 54.1 years (SD=5.09). 85% (n=265) were Caucasian, 47% had prior HRT use and the median months since last menses ranged from 50.7 to 58.2 (See Table 9).

Table 9: Demographics of Patient Population by 1 mg E<sub>2</sub> Treatment Regimens – Studies 102/103

Characteristics	Continuous 1 mg E <sub>2</sub> (N=311)		Cyclophasic 1 mg E <sub>2</sub> / 30 µg NGM (N=313)		Cyclophasic 1 mg E <sub>2</sub> / 90 µg NGM (N=313)		Cyclophasic 1 mg E <sub>2</sub> / 180 µg NGM (N=316)		Total (N=1253)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	53.8	(4.91)	53.8	(5.33)	54.5	(5.13)	54.2	(5.01)	54.1	5.09
Height (cm)	163.9	(6.85)	163.0	(6.68)	163.0	(6.87)	163.2	(6.72)	163.3	6.78
Weight (kg)	69.7	(11.7)	69.1	(11.5)	68.3	(11.3)	69.2	(11.0)	69.1	11.4
Body Mass Index	25.9	(3.7)	26.0	(3.9)	25.7	(3.9)	26.0	(3.7)	25.9	3.8
Median months since last menses	50.7		57.7		58.2		55.9		55.6	
Prior HRT (%)										
No	157 (50%)		170 (54%)		177 (57%)		168 (53%)		168 (54%)	
Yes	154 (50%)		143 (46%)		136 (43%)		148 (47%)		145 (47%)	
Race (%)										
White	268 (86%)		262 (84%)		262 (84%)		270 (85%)		265 (85%)	
Black	7 (2%)		14 (4%)		11 (4%)		13 (4%)		11 (3.5%)	
Asian	0		2 (1%)		3 (1%)		2 (1%)		2 (<1%)	
Other	36 (12%)		35 (11%)		37 (12%)		31 (10%)		35 (11%)	
Smoker (%)										
No	252 (81%)		261 (83%)		265 (85%)		268 (85%)		261 (83%)	
Yes	59 (19%)		52 (17%)		48 (15%)		48 (15%)		52 (16%)	

Source: NDA 21-040, Item 8, Volume 32, adapted from Table 2, page 52.

#### 5.4 Inclusion and exclusion criteria

Study inclusion criteria (NDA 20-040, Item 8, Volume 32, pages 25-25):

- An intact uterus and had not experienced menses without exogenous HRT for at least 12 months prior to the start of treatment;
- Age of 40 to 65 years;
- Serum FSH level  $\geq 40$  mIU/ml or  $\geq 30$  mIU/ml if the women had not received previous HRT and her last spontaneous menstrual period was at least 12 months prior to start of study;
- Serum estradiol concentration of  $\leq 20$  pg/ml;
- No hormone replacement therapy within six weeks prior to screening and eight weeks prior to baseline metabolic testing (Study 102) and dosing (Visit 2);
- Body weight within the  $\pm 35\%$  range for body mass index;
- Overall good health as evidenced by: medical history, ECG, physical examination, laboratory profile (chemistry, hematology including platelet count, and urinalysis, and for Study 102 only: prothrombin time (PT) and activated partial thromboplastin time (APTT), mammogram (unless one had been obtained within 6 months and reported normal), and a gynecologic examination including breast examination and Pap smear with no evidence of dysplasia;
- Signed informed consent form;
- Completed confidential follow-up form;
- High motivation to complete study according to protocol requirements.

Exclusion criteria (NDA 21-040, Item 8, Volume 32, pages 27-28):

- Known or suspected cancer of the breast, endometrial hyperplasia or carcinoma, known or suspected estrogen-dependent neoplasia and other neoplasia (exception of non-recurring basal cell carcinoma of the skin);
- Known or suspected pregnancy;
- Undiagnosed abnormal vaginal bleeding;
- Active thrombophlebitis or thromboembolic disorders;
- History of thrombophlebitis, thrombosis or thromboembolic disorders associated with previous use of ovarian hormones;
- History of cerebral vascular disease, coronary artery disease or myocardial infarction, uncontrolled hypertension, or increased frequency or severity of headaches including migraines;
- Benign or malignant liver disease, gallbladder disease which developed during the use of oral contraceptives or other estrogen-containing products;
- Presence of any neurovascular lesion of the eye or serious visual disturbance;
- Presence of endometrial polyps on screening biopsy;
- Exposure of injectable, or implantable sex steroids within six months of dosing, or to any other injectable or systemic steroid within 30 days of dosing;
- Endocrine disease other than controlled thyroid disease;
- History or presence of chronic alcoholism, drug addiction or severe depression;
- Clinically significant abnormal screening laboratory values;
- Use of the following medications within two weeks of screening: dopaminergic or antidopaminergic drugs, clonidine, digitalis preparations, psychotropic medication, narcotic analgesics, or chronic use of antihistamines;
- Smoking more than 10 cigarettes a day;
- An acute systemic infection within 7 days prior to admission;
- Hypersensitivity or allergy to study drug ingredients;
- Concurrent participation in another clinical trial or receiving an experimental drug or device in the 30 days prior to study medication.

For Study 102 subset:

- Use of aspirin or aspirin-containing products within two weeks prior to laboratory evaluation of coagulation factors;
- Use of lipid, carbohydrate or coagulation altering drugs within two weeks of screening;
- Fasting baseline cholesterol  $\geq 290$  mg/dl, triglycerides  $\geq 250$  mg/dl and glucose  $\geq 140$  mg/dl.

### 5.5 Screening period

During Visit 1A, informed consent was obtained, and a medical and gynecologic history was taken. A physical examination including vital signs, mammogram and electrocardiogram was performed. A screening T<sub>4</sub>, E<sub>2</sub>, FSH, PT, and APTT was performed. The following laboratory analyses were performed after an overnight fast of at least 12 hours: hematology (hemoglobin, hematocrit, RBC, WBC with differential, platelet count), serum chemistry (total bilirubin, alkaline phosphatase, LDH, ALT, AST, BUN, creatinine, albumin, uric acid, phosphorus, calcium, sodium, potassium, chloride, glucose, bicarbonate, total protein, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol), and urinalysis (pH; specific gravity; presence of protein, glucose, ketones and blood; microscopic examination of sediment). Diary cards were distributed.

### 5.6 Baseline period

During Visit 1B, a gynecologic examination (including a breast examination and Pap smear, maturation index (Study 102 only), transvaginal ultrasonography, and endometrial biopsy) was performed. Diary cards were collected and reviewed and additional diary cards were distributed.

During the Baseline period (14 consecutive days prior to randomization) and throughout the first three months of treatment, subjects recorded the number of hot flushes (by severity – mild, moderate, or severe) and number of waking episodes (night sweats) daily. Waking episodes were recorded only if associated with hot flushes or perspiration and were summarized as severe hot flushes.

Vaginal wall epithelial smears for the determination of maturation index were obtained at the pretreatment visit and Visit 5 (Month 7).

Endometrial biopsies performed during Visit 1B (Baseline) and Visit 7 (Month 12) were obtained using procedures consistent with the current clinical practice at the study site. All biopsy specimens were sent to \_\_\_\_\_ for processing and for the initial safety reading. Subjects with hyperplasia at screening were not enrolled or, if diagnosed while on treatment, were discontinued from study medication and given appropriate treatment and follow-up. If biopsies yielded insufficient tissue for diagnosis and the endometrium thickness determined by ultrasonography was greater than 5 mm, the transvaginal ultrasonography (TVU) and endometrial biopsy were to be repeated. Safety readings of the biopsies were made immediately available to investigators, and they served as the basis for clinical management of the study subjects as results of the efficacy readings were not available until the data base had been released and all study data unblinded.

Two pathologists (PA1 and PA2) read the biopsy specimens for efficacy. In cases where these two pathologists differed as to the presence of hyperplasia, the specimens in question were read by a third pathologist (PA3) who served as adjudicator. Slides sent to PA 3 were supplemented with "filler" slides in approximately the same quantity as the slides in question.

If the readings of PA1 and PA2 represented different "normal tissue" diagnoses, the reading of PA1 was included in the data set. An exception was that if one pathologist read "no endometrial tissue" or "no endometrial tissue obtained" and the other pathologist read a specific type of normal tissue, then the latter reading was included in the derived data set.

If all three pathologists read a biopsy specimen, and the reading of two represented normal tissue while the third represented hyperplasia, then a normal tissue result was included in the derived data set, with the specific type of normal tissue taken from the first pathologist giving a normal tissue reading using the ranking PA1>PA2>PA3.

In cases where two out of the three pathologists gave readings of different types of hyperplasia (or cancer), the reading representing the most severe type of pathology was recorded in the derived data set.

### 5.7 Treatment period

All study medications were provided by RWJPRI as identically appearing white, oval tablets in blister cards. Each blister card contained 30 tablets (five rows of six tablets each). The combined E<sub>2</sub>/NGM tablets, as well as the estradiol-alone tablets, were manufactured by a dry-blend manufacturing process to be used in the commercial production of the tablets.

Prior to randomization and dispensing of study medication, participants in Study 102 had blood samples drawn after at least a 12 hour fast for the following tests:

- Total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, HDL<sub>2</sub>-cholesterol, HDL<sub>3</sub>-cholesterol, triglycerides, Apolipoprotein A-1, Apolipoprotein B, and Lipoprotein (a).
- Prothrombin time, activated partial thromboplastin time, Factors VII and X, antithrombin III (functional assay), plasminogen (functional assay), Protein S (functional assay), and fibrinogen.
- Fasting insulin and glucose (in samples drawn prior to glucose load), and glucose tolerance test (100 gram oral glucose load).

Following Study Day 1, subjects returned to the study site for six additional visits. At Visit 3 (Month 2), Visit 4 (Month 4), and Visit 6 (Month 10) vital signs were obtained and diary cards were collected and reviewed for concomitant medication, number and severity of hot flushes (first three months of treatment), and adverse events. Additional diary cards and study drugs were dispensed during these visits.

At Visit 5 (Month 7), in addition to the same evaluations conducted during Visits 3, 4, and 6, a physical and gynecologic examination (including Pap smear and maturation index) were repeated, and the same clinical laboratory evaluations and metabolic parameters, as mentioned above, were collected.

At the end-of-treatment visit, Visit 7 (Month 12), or at early withdrawal, all Visit 5 evaluations and tests were repeated, and a transvaginal ultrasonography and endometrial biopsy was performed. An end-of-study mammogram was also performed.

Visit 8 (Study Days 371-380, final study visit) was completed to review diary card for bleeding, concomitant medication, and adverse events recorded for a one-month period post treatment.

### 5.8 Evaluation period

During the pretreatment period (at least 14 days prior to randomization) and throughout the double-blind treatment period, subjects recorded in diary cards their daily study drug use, use of concomitant medication, adverse events, and the frequency and severity of vaginal bleeding. The number and severity of hot flushes were recorded for the first three months of Study 102 and 103 (see NDA 21-040, Item 8, Volume 32, page 37 for a full description of hot flush severity). The criterion for efficacy for vasomotor symptoms was a reduction in the frequency and severity of vasomotor symptoms at the end of three months compared to baseline.

In Study 102, vaginal wall epithelial smears were obtained pretreatment and Visit 5 (Month 7) and analyzed by <sup>1</sup> Efficacy would be indicated by a change in the maturation index to reflect a "shift to the right" in the percentages of parabasal/intermediate/superficial cells at Month 7 compared to baseline.

The frequency and severity of vaginal bleeding was recorded during treatment and for one month post-treatment (see NDA 21-040, Item 8, Volume 32, page 37 for a full description of spotting/bleeding). Since no prospective efficacy criteria for vaginal bleeding were specified, only descriptive summaries of data were used to compare the incidence and pattern of bleeding associated with the various treatment regimens.

For the primary efficacy criterion, the reduction in the incidence of estrogen-induced endometrial hyperplasia in the cyclophasic groups as compared to the estrogen-only groups, the number of cases of all hyperplasia and endometrial cancer were combined within each group to determine the incidence of estrogen-induced hyperplasia associated with each treatment regimen.

### 5.9 Withdrawals and compliance

A total of 352 subjects were enrolled at 18 US centers in Study 102 while a total of 1,543 subjects were enrolled at 65 US centers, 1 center in Puerto Rico and 1 center in Costa Rica in Study 103. Of the total 1,895 subjects enrolled into Studies 102/103, 631 subjects were randomized to receive one of three 2mg E<sub>2</sub> regimens and 1,264 subjects were randomized to received one of four 1 mg E<sub>2</sub> regimens. The three 2 mg E<sub>2</sub> regimens were discontinued while enrollment was in progress and only 5-6% of the subjects assigned to the 2 mg E<sub>2</sub> regimens completed the study.

As shown in Table 10, the number of subjects randomized to the 1 mg E<sub>2</sub> regimens ranged from 314 to 319 per regimen, and study completion rates ranged from 68% (n=215) for the continuous 1 mg E<sub>2</sub> regimen to 79% (n=249) for the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 ug NGM regimen. Sixty-nine percent of subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 ug NGM and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 ug NGM regimens completed the study (n=219 and 220, respectively).

Table 10: Enrollment, Completion, and Withdrawal Information for Subjects Randomized to the 1mg E<sub>2</sub> regimens on Studies ESTNRG-CHRT-102/103

	Continuous 1 mg E <sub>2</sub> No. (%) <sup>a</sup>	Cyclophasic 1 mg E <sub>2</sub> / 30 ug NGM No. (%) <sup>a</sup>	Cyclophasic 1 mg E <sub>2</sub> / 90 ug NGM No. (%) <sup>a</sup>	Cyclophasic 1 mg E <sub>2</sub> / 180 ug NGM No. (%) <sup>a</sup>	Total No. (%) <sup>a</sup>
No. Randomized	315	314	316	319	1264
No. Completed	215 (68%)	249 (79%)	219 (69%)	220 (69%)	903 (71.4%)
No. Withdrawn	100 (32%)	65 (21%)	97 (31%)	99 (31%)	361 (28.6%)
Reasons for Withdrawal					
Lost to follow-up	7 (2%)	6 (2%)	9 (3%)	9 (3%)	31 (2.5%)
Adverse event	49 (16%)	19 (6%)	23 (7%)	27 (8%)	118 (9.3%)
Bleeding <sup>b</sup>	6	2	2	13	23
Endo. Hyperplasia <sup>b</sup>	34	3	1 <sup>c</sup>	0	38
Subject choice	35 (11%)	27 (9%)	49 (16%)	58 (18%)	169 (13.4%)
Bleeding	21	13	37	43	114
Other subject choice	14	14	12	15	55
Other reason	8 (3%)	13 (4%)	15 (5%)	5 (2%)	41 (3.2%)
Missing reason	1 <sup>d</sup> (<1%)	0 (0%)	1 <sup>d</sup> (<1%)	0 (0%)	2 (<1%)

<sup>a</sup> Percentage of the number of subjects enrolled (randomized to treatment) in the group.

<sup>b</sup> Bleeding and endometrial hyperplasia do not constitute all of the adverse events leading to withdrawal but are represented because they were the most frequent. Also they are not mutually exclusive.

<sup>c</sup> Subject 36002 (Parker) was discontinued due to endometrial hyperplasia diagnosed on D&C specimen evaluated at a local laboratory.

<sup>d</sup> CRF records were not completed for Subjects 14025 and 14023 (Fiddes) when site was discontinued.

Source: NDA 21-040, Item 8 Volume 32, adapted from Table 3, page 56.

As shown in Table 10, 13.4% (n=169 of 1264) of subjects receiving one of the four 1 mg E<sub>2</sub> regimens withdrew because of subject choice, primarily bleeding, and 9.3% (n=118) withdrew because of adverse events (including endometrial hyperplasia). Adverse events leading to subject withdrawal will be discussed in the Safety Analysis section of this review.

Bleeding, as a reason for withdrawal, was classified either in the category of adverse event or as subject choice at the discretion of the investigator and as shown above was categorized most frequently under subject choice. Combining the categories of adverse event and subject choice for bleeding and

comparing incidence of discontinuation for bleeding shows rates (in descending order) of 18% (56 of 319 subjects), 12% (39 of 316), 9% (27 of 315), and 5% (15 of 314) for the 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM, 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM, continuous 1mg E<sub>2</sub>, and 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM regimens respectively.

Treatment compliance was assessed from diary card data. The number and percentage of subjects who missed at least one tablet of study medication during each month of treatment and the mean number of tablets missed in each month was analyzed. Compliance was similar among the four groups of subjects receiving the 1 mg E<sub>2</sub> regimens. In each of these four groups, tablets were missed by ≤ 40% of subjects in any month and the mean number of tablets missed was ≤ 1.4 per month (NDA 21-040, Item 8, Volume 32, page 57).

#### 5.10 Protocol deviations

Documentation in the study files indicates that a number of subjects were allowed to enter the study with slight deviations from inclusion/exclusion criteria, namely, outside the specific limits for BMI, E<sub>2</sub> concentration, FSH concentration, and blood pressure limits.

Twenty-six subjects (receiving the 1 mg E<sub>2</sub> regimens) were enrolled with baseline estradiol values greater than 20 pg/ml. One major violation of entry E<sub>2</sub> value occurred in Study 103 (Subject 52005) with a baseline value of 163 pg/ml measured 16 days prior to Day 1. Two subjects had FSH levels below 30 mIU/ml (29.6 and 29.4).

Two major protocol violations involving concomitant medication occurred in Study 102. One subject (Subject 6024) in the continuous 1 mg E<sub>2</sub> group was treated with the lipid-lowering drug Pravachol® during the last five days of the study and was included in the analysis of lipid data. Subject 6021 in the 1 mg E<sub>2</sub>/90 µg NGM group took prednisone for the last three months of the study, which may have contributed to the elevated fasting insulin value at cycle 12 for this subject.

#### 5.11 Efficacy analysis

The primary efficacy criterion was the reduction in the incidence of estrogen-induced endometrial hyperplasia in the cyclophasic groups as compared to the estrogen-only groups. As previously discussed, the efficacy summaries and analyses are presented for the four regimens containing 1 mg of E<sub>2</sub> (efficacy summaries and analyses for the 2 mg E<sub>2</sub> groups are not presented). The number of cases of simple and complex hyperplasia, hyperplasia with cytological atypia, and endometrial cancer were combined within each group to determine the incidence of estrogen-induced hyperplasia associated with each treatment regimen.

Endometrial biopsies were obtained prior to treatment and at the end-of-study or at early withdrawal. One thousand and ten (1,010) subjects in the 1 mg E<sub>2</sub> groups had biopsy results available after the start of treatment (243 subjects did not) and are included in the intent-to-treat analysis. However, 56 of the 1010 endometrial biopsies showed either "no tissue obtained" or "no endometrial tissue obtained." It is assumed, however, that in these 56 cases a valid attempt was made to sample the endometrium yet no definitive endometrial histology results were obtained. For the purpose of this review, these 56 biopsy results have been excluded from Table 11.

Hyperplasia was diagnosed for 74 (28.9%) of 256 subjects in the 1 mg E<sub>2</sub>-only group and 16 (6.5%) of 244 subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM group. No case of endometrial hyperplasia was diagnosed among the 227 subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM group or among the 227 subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM group. In the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen proposed for marketing, the estimated incidence of hyperplasia is 0.00050%, and the upper limit of the 95% confidence interval is less than 1%.

Table 11: Incidence of Endometrial Hyperplasia in Final Evaluable Biopsy Results for Studies 102/103; Intent-to-Treat Population

Patient	Continuous 1 mg E <sub>2</sub>	Cyclophasic 1 mg E <sub>2</sub> / 30 mg NGM	Cyclophasic 1 mg E <sub>2</sub> / 90 mg NGM	Cyclophasic 1 mg E <sub>2</sub> / 180 mg NGM
Total number of patients, Intent-to-Treat Population	265	260	242	243
Number (%) of patients with evaluable biopsies <sup>a</sup>	256 (96.6%)	244 (93.8%)	227 (93.8%)	227 (93.4%)
Number (%) of subjects with evaluable biopsies No hyperplasia	182 (71%)	228 (93.4%)	227 (100%)	227 (100%)
Hyperplasia	74 (29%) <sup>b</sup>	16 (6.5%) <sup>c</sup>	0 (0%) <sup>*</sup>	0 (0%) <sup>†</sup>

Biopsies with tissue specific diagnoses excluding biopsies classified as "no tissue obtained" or "no endometrial tissue obtained" and biopsies with endometrial thickness measurements not obtained on the same day as the endometrial biopsy or biopsies originating from Dr. Kipperman's site (Study 103).

- <sup>b</sup> Includes subjects with simple hyperplasia (n=64), complex hyperplasia (n=2), and hyperplasia with cytological atypia (n=8).
- <sup>c</sup> Includes subjects with simple hyperplasia (n=14), complex hyperplasia (n=1), and hyperplasia with cytological atypia (n=1).
- <sup>\*</sup> Estimated incidence of hyperplasia is 0.00050% with the upper limit of the 95% confidence interval < 1%.
- <sup>†</sup> Estimated incidence of hyperplasia is 0.00051% with the upper limit of the 95% confidence interval < 1%.

Source: Adapted from NDA 21-040, Item 8, Volume 32, Table 7, page 64.

#### Reviewer's comments

Per the sponsor, subjects with insufficient tissue (no tissue obtained, no endometrial tissue obtained, or not evaluable) at final endometrial biopsy in Studies 102/103 were not assumed to have inactive/atrophic tissue for the purpose of analysis. Instead, an imputation was made of each subject's endometrial status (hyperplasia or no hyperplasia) based on the endometrial thickness measurement, if such measurement was performed on the same day as the endometrial biopsy. If an endometrial thickness of  $\geq 5$  mm was obtained, the subject was assigned to the category of imputed hyperplasia, and if less than 5 mm, the subject was assigned to the category of imputed no hyperplasia. In the four 1 mg E<sub>2</sub> treatment arms, a total of 20 subjects with insufficient tissue upon biopsy and with endometrial thickness by transvaginal ultrasound of  $\geq 5$  mm were categorized as imputed hyperplasia, 28 were categorized as imputed no hyperplasia (endometrial thickness of < 5 mm), and 8 were categorized as not evaluable because either the endometrial thickness measurement and the endometrial biopsy were not performed on the same day or the measurement originated from Dr. Kipperman's site, Study 103 (ultrasound not calibrated). The sponsor's imputation of hyperplasia or no hyperplasia based on endometrial thickness measurement, while interesting, does not offer a definitive diagnosis for 56 subjects. Published literature comparing endometrial thickness and biopsy observed endometrial pathology is limited at present and no definitive correlation can be drawn.

Data submitted from these studies, however, clearly indicate that 90  $\mu$ g of norgestimate is the lowest, effective NGM dose for administration with 1 mg E<sub>2</sub> to protect the endometrium from developing hyperplasia (based on 954 biopsies with tissue specific diagnoses).

Based on data from subjects in the 1 mg E<sub>2</sub> groups with 12 months of bleeding/spotting data in Studies 102 and 103, the percentage of subjects who reported no bleeding/spotting from Months 1-12 of treatment are as follows: 44% in the 1 mg E<sub>2</sub> group (92 of 211 subjects), 37% in the 1mg E<sub>2</sub>/1mg E<sub>2</sub>+30 mg NGM group (89 of 243 subjects), 23% in the 1mg E<sub>2</sub>/1mg E<sub>2</sub>+90 mg NGM group (49 of 211), and 20% in the 1mg E<sub>2</sub>/1mg E<sub>2</sub>+180 mg NGM group (43 of 212). For each month of the study

the percentage becoming bleeding/spotting free increased slightly at each month. In the last six months of treatment (Months 7 to 12) the percentages were 54% in the 1 mg E<sub>2</sub> group (113 of 211), 48% in the 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 mg NGM group (116 of 243), 36% in the 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 mg NGM group (77 of 211), and 36% 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 mg NGM group (76 of 212). At Month 12 the percentages were 74% (156 of 211), 72% (174 of 243), 56% (118 of 211), and 54% (115 of 212), respectively (NDA 21-040, Item 8, Volume 32, Table 13, Page 70).

The sponsor also compared the overall daily incidence and severity of bleeding/spotting for each treatment group. The overall daily incidence and severity of bleeding/spotting was lowest for the 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 mg NGM group (see NDA 21-040, Item 8, Volume 32, Attachments 7.3, 7.4, 7.5, and 7.6, pages 305 to 310).

#### Reviewer's comments

The percentage of subjects without bleeding/spotting was similar for the 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 mg NGM and 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 mg NGM groups at Month 12 (56% and 54%, respectively). During the early months of treatment, however, the 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 mg NGM group had a slightly higher percentage of subjects free of bleeding/spotting at each month through Month 7 (35.1% and 32.5%, respectively) than the 1mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 mg NGM group.

Overall, the most favorable amenorrhea patterns at Month 12 were found in the continuous 1 mg E<sub>2</sub> group (74%) and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM group (72%).

In Studies 102/103, subjects completed daily diary cards to record hot flushes/waking episodes during a baseline period and for the first 90 days of treatment. Subjects who were both symptomatic and asymptomatic were enrolled (with and without hot flushes). Although enrollment criteria did not meet the Agency's guidance for relief of vasomotor symptoms clinical trials (per the Guidance, entry criteria should require enrolled subjects to have a minimum of 7 to 8 moderate-to-severe hot flushes per day or at least 60 per week at baseline), results across the four 1 mg E<sub>2</sub> treatment groups for moderate or severe hot flushes (any baseline frequency, excluding mild hot flushes) showed that there were no statistically significant differences for mean change between groups as shown below:

Treatment group:	1 mg E <sub>2</sub> , N=301	1/30 µg NGM, N=301	1/90, N=303	1/180, N=306
Baseline Mean	2.2	2.3	2.2	2.6
Mean Change (SD)	-2.0 (3.72)	-2.1 (2.83)	-2.0 (3.24)	-2.2 (4.24)

The point estimate and 95% confidence interval for treatment difference, based on analysis of covariance, for continuous 1mg E<sub>2</sub> versus 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM is 0.03 (-0.21, 0.27) (see NDA 21-040, Item 8, Volume 32, page 80).

Upon request by the Division, the sponsor submitted, on June 10, 1999, a post-hoc analysis of the mean change in the mean daily number of moderate-to-severe hot flushes during therapy for subjects with a mean baseline moderate-to-severe hot flush number of ≥ 7 per day. The results, at Week 12, are shown below:

Treatment group:	1 mg E <sub>2</sub> , N=29	1/30 µg NGM, N=27	1/90, N=26	1/180, N=37
Mean Change (SD)	-9.9 (7.06)	-8.7 (3.18)	-10.2 (4.34)	-10.4 (3.60)

The point estimate and 95% confidence interval for treatment difference, based on analysis of covariance, for continuous 1 mg E<sub>2</sub> versus 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM is 0.50 (-1.10, 2.11).

On August 5, 1999, upon request of the Division, the sponsor analyzed and submitted changes in the mean number of moderate-to-severe hot flushes for all subjects in the 1 mg E<sub>2</sub> groups who entered the study with at least 7 moderate-to-severe hot flushes per day at baseline. Table 12 represents the results of this analysis.

Table 12: Change in the Mean Number of Moderate-to-Severe Hot Flushes during Therapy in All Subjects with  $\geq 7$  Moderate-to-Severe Hot Flushes at Baseline, Studies 102/103

Week	1 mg E <sub>2</sub> N=29 of 301 (10%)	1 mg E <sub>2</sub> /30 $\mu$ g NGM N=27 of 301 (9%)	1 mg E <sub>2</sub> /90 $\mu$ g NGM N=26 of 304 (8.6%)	1 mg E <sub>2</sub> /180 $\mu$ g NGM N=37 of 306 (12%)
Baseline				
Mean #	10.99	10.13	10.86	11.48
Week 4				
Mean #	3.33	2.68	2.60	1.38
Mean Change	-7.66	-7.46	-8.26	-9.40
Week 8				
Mean #	1.10	1.71	0.88	0.28
Mean Change	-9.88	-8.43	-10.16	-10.51
Week 12				
Mean #	1.13	1.13	0.71	0.12
Mean Change	-9.85	-9.01	-10.17	-10.74

Source: Adapted from information provided by the sponsor August 5, 1999 following a Division request for information, and from NDA 21-040, Item 8, Volume 32, Tables 20 & 21, pages 79-80.

The estimated difference and p-value for the continuous 1 mg E<sub>2</sub> versus the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90  $\mu$ g NGM regimen at Weeks 4, 8, and 12 (based on least squares estimates of the mean change from the analysis of covariance) are as follows, respectively: -0.006 (p=0.995), 0.089 (p=0.898), and 0.736 (p=0.201). The only statistically significant difference from the continuous 1 mg E<sub>2</sub> dose is noted at Week 12 in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180  $\mu$ g NGM regimen (estimated difference of 1.173, p=0.033).

#### Reviewer's comments

In Studies 102/103 subjects were not required to have hot flushes at baseline. However, study participants recorded hot flush number and severity daily on diary cards for the first 12 weeks of treatment. For the subjects who did report baseline hot flushes (any frequency, excluding mild hot flushes), the mean number of moderate-to-severe hot flushes at baseline ranged between 2.2 and 2.6 across the four 1 mg E<sub>2</sub> groups. The mean change across the four 1 mg E<sub>2</sub> groups were similar at Week 12.

The same similarity in mean change across the four 1 mg E<sub>2</sub> groups was seen for the post-hoc subgroup of subjects who entered the study with  $\geq 7$  moderate-to-severe hot flushes per day. At 12 weeks, the mean change in moderate-to-severe hot flushes ranged between -8.7 (1/30 regimen) and -10.4 (1/180 regimen). The point estimate and 95% confidence interval for treatment difference (based on an analysis of covariance) between continuous 1 mg E<sub>2</sub> and cyclophasic 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90  $\mu$ g NGM was 0.50 (-1.10, 2.11).

As presented in Table 12, between 8.6% and 12% of the subjects reporting moderate-to-severe hot flushes had at least 7 moderate-to-severe hot flushes per day at baseline. While this represents a limited number of the total study population, the post hoc analysis of this subgroup population demonstrates that the magnitude of change over 4, 8, and 12 study weeks was similar in each group (based on least square estimate of the mean change from the analysis of covariance). At Weeks 4, 8, and 12, the estimated difference between 1 mg E<sub>2</sub> alone and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90  $\mu$ g NGM regimen was not statistically significant.

Data on maturation index was collected in Study 102 only. Results summarized in Table 13 for subjects with data available at both pretreatment and Month 7 show large decreases in the percentages of parabasal cells while the percentages of both intermediate and superficial cells increased.

Table 13: Summary of Maturation Index Results, Study 102/103

	Baseline Mean	Month 7 Mean	Mean Change
<b>1 mg E<sub>2</sub> Group (n=37)</b>			
Parabasal Cells (%)	25.1	2.7	-22.4
Intermediate Cells (%)	69.2	76.4	7.2
Superficial Cells (%)	5.7	20.9	15.3
<b>1 mg E<sub>2</sub>/30 µg NGM (n=37)</b>			
Parabasal Cells (%)	27.2	1.9	-25.3
Intermediate Cells (%)	69.3	76.2	6.9
Superficial Cells (%)	3.5	21.9	18.4
<b>1 mg E<sub>2</sub>/90 µg NGM (n=32)</b>			
Parabasal Cells (%)	31.9	0.0	-31.9
Intermediate Cells (%)	64.2	80.9	16.7
Superficial Cells (%)	3.9	19.1	15.2
<b>1 mg E<sub>2</sub>/180 µg NGM (n=37)</b>			
Parabasal Cells (%)	45.7	0.0	-45.7
Intermediate Cells (%)	50.3	83.9	33.6
Superficial Cells (%)	4.1	16.1	12.1

Source: NDA 21-040, Item 8, Volume 32, page 83

#### Reviewer's comments

In Table 13, the results appear to demonstrate a dose response. However, among the cyclophasic HRT groups, the p-value for the difference from the continuous 1 mg E<sub>2</sub> group (as determined by two-way analysis of variance on ranks) are not statistically significant (p=0.817 for 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM, P=0.494 for 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM, and p=0.139 for 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM).

#### 5.12 Safety analysis.

Adverse event data were reported for 1874 subjects among the seven treatment groups (1252 subjects in the 1 mg E<sub>2</sub> groups and 622 subjects in the 2 mg E<sub>2</sub> groups). A discussion of deaths, other serious adverse events, and treatment-emergent adverse events follows below.

#### Deaths

One subject died during the study and one subject died 3-1/2 months post-treatment.

Subject 84005: 49-year old woman in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM group, collapsed on study day 146 and was hospitalized in a semi-comatose condition. A CT scan revealed a subarachnoid hemorrhage affecting the brain stem, lateral ventricles, and basal ventricle and patient was placed on life support. Life support was stopped at the family's request five days later, with subsequent death. The subject's medical history indicated no relevant cardiovascular or neurologic history. The event was evaluated by the investigator as having an unlikely relationship to the treatment.

Subject 25001: 63-year old woman in the 2 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM group had been discontinued from study therapy on study day 294 due to sponsor termination of the 2 mg regimens. Two months later, she experienced a stroke and had by-pass subclavian and carotid artery surgery. She was found dead in her apartment one month later. She had a history of hypertension and migraines under treatment, and a history of hypercholesterolemia. The subject had taken Estrace® and Provera® as HRT for four years prior to enrollment in the study. The event was evaluated as having an unlikely relationship to the study treatment.

#### Other Serious Adverse Events

Other serious adverse events were reported for 234 subjects in Studies 102/103. The majority (175) of reports were for endometrial hyperplasia (with or without other adverse events) based on the safety reading (not the efficacy readings) of the biopsies. As previously mentioned in Section 5.6 of this

review, safety reading were readings immediately available to investigators, and they served as the basis for the clinical management of the study subjects. One hundred thirty-nine (139) of the 176 safety reports of endometrial hyperplasia were reported from the continuous 1 mg (83 subjects) and 2 mg E<sub>2</sub> (56 subjects) groups. Endometrial hyperplasia (via the safety readings) was also reported for 30 subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM group. The remaining six cases were seen in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM, and 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+90 µg NGM groups (3, 2, and 1 case, respectively).

Among the remaining reports of serious adverse events were nine reports of cancer diagnosed during or after the study. Four subjects were diagnosed with breast cancer (one each in 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM groups; and the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group). In addition to the four definite reports of breast cancer, one subject in the continuous 1 mg E<sub>2</sub> group was diagnosed with a breast neoplasm that was a borderline lesion between atypical intraductal hyperplasia and cribriform intraductal carcinoma. Five additional cancers were diagnosed including one multiple myeloma, one basal cell carcinoma, one metastatic adenocarcinoma from a primary lung cancer, one cervical cancer, and one metastatic colon cancer two months after completion of study treatment.

Two subjects in the 2 mg E<sub>2</sub> groups had myocardial infarctions (one subject was being treated for hypertension and one subject had had a previous MI and a blocked artery on sonogram). One subject in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM, group developed mitral insufficiency requiring mitral valve replacement.

There were six reports of cholelithiasis in the 1 mg E<sub>2</sub> groups (1 each in the 1 mg E<sub>2</sub> group and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM group, and 4 in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM, group), and none in the 2 mg groups. Three cases of cholecystitis were also reported (one in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group, and one each in the 2 mg continuous group and the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM, group). Eight of these nine subjects had cholecystectomies (four of the five subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group had cholecystectomies).

One subject (Subject 42014) with a history of asthma and emphysema, experienced unusual symptoms including chest pain, headache, and muscle spasm after dosing with the study drug.

There were no reports of pulmonary embolism, although there were three reports of superficial phlebitis.

#### Reviewer's comments

Of concern is the imbalance in the number of reported cases of cholelithiasis or cholecystitis and the number of cholecystectomies among the seven treatment groups. Of the nine reports of cholelithiasis or cholecystitis, five cases occurred in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group and four of these five subjects had cholecystectomies. While these numbers do not indicate a higher incidence of gallbladder disease and cholecystectomies with Ortho-Prefest™ than reported in other studies, they warrant close post-marketing surveillance.

#### Treatment-Emergent Adverse Events

In Studies 102/103, treatment-emergent adverse events were reported by 1088 (87%) of the 1252 subjects enrolled and percentages were similar across the four 1 mg E<sub>2</sub> groups (84 to 89%). For the 2 mg E<sub>2</sub> groups, treatment emergent adverse events were reported by 504 (81%) of 622 subjects. As shown in Table 14, the most frequently occurring adverse events in the 2 mg E<sub>2</sub> groups were breast pain, upper respiratory tract infection, headache, dysmenorrhea, and abdominal pain. Among the adverse events shown in Table 14 for the 1 mg E<sub>2</sub> groups, the most frequently occurring events included upper respiratory tract infection, headache, breast pain, dysmenorrhea, back pain, and abdominal pain.

Table 14: Adverse Events Reported with an Incidence of ≥ 5% in Any Treatment Group, Summarized by Body System and Preferred Terms<sup>a</sup>

Body System Preferred Term	1 mg E <sub>2</sub> (N=311) N (%)	1 mg E <sub>2</sub> /30 µg NGM (N=312) N (%)	1 mg E <sub>2</sub> /90 µg NGM (N=313) N (%)	1 mg E <sub>2</sub> /180 µg NGM (N=316) N (%)	2 mg E <sub>2</sub> (N=207) N (%)	2 mg E <sub>2</sub> /90 µg NGM (N=213) N (%)	2 mg E <sub>2</sub> /180 µg NGM (N=202) N (%)
<b>Reproductive disorder</b>							
Breast pain	41 (13%)	64 (21%)	61 (19%)	58 (18%)	46 (22%)	53 (25%)	75 (37%)
Dysmenorrhea	40 (13%)	43 (14%)	36 (12%)	51 (16%)	31 (15%)	24 (11%)	31 (15%)
Leukorrhea	18 (6%)	18 (6%)	11 (4%)	6 (2%)	14 (7%)	7 (3%)	5 (2%)
Vaginal hemorrhage <sup>b</sup>	18 (6%)	8 (3%)	9 (3%)	21 (7%)	32 (15%)	19 (9%)	19 (9%)
Vaginitis	34 (11%)	43 (14%)	23 (7%)	23 (7%)	19 (9%)	19 (9%)	19 (9%)
<b>Body as a Whole</b>							
Edema generalized	10 (3%)	21 (7%)	10 (3%)	9 (3%)	10 (5%)	7 (3%)	13 (6%)
Back pain	53 (17%)	41 (13%)	39 (12%)	40 (13%)	16 (8%)	14 (7%)	20 (10%)
Fatigue	9 (3%)	18 (6%)	21 (7%)	16 (5%)	8 (4%)	10 (5%)	9 (4%)
Pain	23 (7%)	18 (6%)	14 (4%)	6 (2%)	7 (3%)	4 (2%)	8 (4%)
Influenza-like syndrome	31 (10%)	35 (11%)	37 (12%)	17 (5%)	9 (4%)	5 (2%)	12 (6%)
Injury	15 (5%)	15 (5%)	7 (2%)	16 (5%)	5 (2%)	2 (1%)	2 (1%)
<b>Respiratory disorders</b>							
Pharyngitis	18 (6%)	14 (4%)	16 (5%)	12 (4%)	5 (2%)	6 (3%)	5 (2%)
Sinusitis	30 (10%)	36 (12%)	31 (10%)	34 (11%)	19 (9%)	11 (5%)	12 (6%)
Upper tract infection	95 (31%)	88 (28%)	91 (29%)	66 (21%)	35 (17%)	34 (16%)	29 (14%)
Bronchitis	4 (1%)	23 (7%)	9 (3%)	18 (6%)	2 (1%)	3 (1%)	2 (1%)
<b>Gastrointestinal system disorders</b>							
Diarrhea	17 (5%)	20 (6%)	15 (5%)	7 (2%)	9 (4%)	6 (3%)	8 (4%)
Abdominal pain	38 (12%)	39 (13%)	44 (14%)	37 (12%)	30 (14%)	18 (8%)	26 (13%)
Dyspepsia	16 (5%)	14 (4%)	17 (5%)	21 (7%)	13 (6%)	6 (3%)	11 (5%)
Flatulence	16 (5%)	22 (7%)	24 (8%)	19 (6%)	9 (4%)	10 (5%)	14 (7%)
Nausea	14 (5%)	24 (8%)	20 (6%)	17 (5%)	17 (8%)	11 (5%)	9 (4%)
<b>Central/peripheral nervous system disorder</b>							
Dizziness	4 (1%)	10 (3%)	17 (5%)	10 (3%)	10 (5%)	9 (4%)	2 (1%)
Headache	63 (20%)	54 (17%)	61 (19%)	55 (17%)	25 (12%)	30 (14%)	34 (17%)
<b>Musculoskeletal system disorders</b>							
Arthralgia	29 (9%)	29 (9%)	21 (7%)	21 (7%)	8 (4%)	7 (3%)	7 (3%)
Myalgia	24 (8%)	23 (7%)	25 (8%)	22 (7%)	8 (4%)	14 (7%)	11 (5%)
<b>Psychiatric disorders</b>							
Depression	22 (7%)	15 (5%)	16 (5%)	29 (9%)	7 (3%)	10 (5%)	13 (6%)
<b>Urinary tract disorders</b>							
Urinary tract infection	14 (5%)	16 (5%)	11 (4%)	13 (4%)	6 (3%)	2 (1%)	3 (1%)
<b>Metabolic/nutritional</b>							
Weight increase	17 (5%)	18 (6%)	11 (4%)	14 (4%)	10 (5%)	9 (4%)	12 (6%)

<sup>a</sup> Excluding endometrial hyperplasia.

<sup>b</sup> Vaginal hemorrhage is the preferred term used to code verbatim reports of vaginal bleeding. Source: NDA 21-040, Item 8, Volume 32, Table 28. Pages 88-89

Adverse events occurring with a subject incidence of > 15% in any group are shown below:

	1 mg E <sub>2</sub> 1/30 (N=311)	1/90 (N=312)	1/180 (N=313)	1/180 (N=316)	2 mg E <sub>2</sub> 2/90 (N=207)	2/180 (N=213)	2/180 (N=202)
Upper respiratory tract infection	31%	28%	29%	21%	17%	16%	14%
Headache	20%	17%	19%	17%	12%	14%	17%
Breast pain	13%	21%	19%	18%	22%	25%	37%
Dysmenorrhea	13%	14%	12%	16%	15%	11%	15%
Back pain	17%	13%	12%	13%	8%	7%	10%

**Reviewer's comments**

Headache, breast and back pain, and dysmenorrhea are consistent with adverse events expected for ERT and HRT regimens. Upper respiratory tract infection, not commonly associated with HRT use, may be influenced by multiple factors including uncontrolled environmental factors.

The number and percentage of subject who discontinued the study treatment due to adverse events are shown in Table 15. Discontinuations were highest in the two groups receiving continuous E<sub>2</sub> and were higher for the 2 mg E<sub>2</sub> group (22%) than the 1 mg E<sub>2</sub> group (16%). Overall, the percentage discontinuing in each 2 mg group was higher (14.3%) than the percentage discontinuing in the corresponding (same NGM dose) 1 mg group, even though the average treatment exposure was less in the 2 mg E<sub>2</sub> groups.

Table 15: Number of Subjects Discontinuing in Studies 102/103 Due to One or More Adverse Events in Each Treatment Group

Treatment Group	N	n	%
Continuous 1 mg E <sub>2</sub>	311	49	(16)
Cyclophasic 1 mg E <sub>2</sub> /30 ug NGM	312	19	(6)
Cyclophasic 1 mg E <sub>2</sub> /90 ug NGM	313	23	(7)
Cyclophasic 1 mg E <sub>2</sub> /180 ug NGM	316	27	(9)
Continuous 2 mg E <sub>2</sub>	207	46	(22)
Cyclophasic 2 mg E <sub>2</sub> /90 ug NGM	213	23	(11)
Cyclophasic 2 mg E <sub>2</sub> /180 ug NGM	202	20	(10)

Source: NDA 21-040, Item 8, Volume 32, Table 33, page 102

Endometrial hyperplasia (safety reading) was the adverse event reported most (n=38[3%]), followed by vaginal bleeding (n=23[2%]) as reasons for discontinuation in the 1 mg E<sub>2</sub> groups. The reverse was true for the 2 mg E<sub>2</sub> groups: 7% (n=41) for vaginal bleeding and 3.4% (n=21) for safety reading endometrial hyperplasia.

**Reviewer's comments**

It is somewhat difficult to quantitatively compare adverse events in the 2 mg E<sub>2</sub> groups with those of the 1 mg E<sub>2</sub> groups due to the shorter average treatment duration in the 2 mg E<sub>2</sub> groups. Nonetheless, the sponsor's decision to discontinue the 2 mg E<sub>2</sub> groups, due to adverse events, seems warranted.

**Metabolic and Coagulation Results**

Results of metabolic and coagulation tests conducted in Study 102 for the four 1 mg E<sub>2</sub> groups demonstrated a mean percent increase in HDL-Cholesterol for the continuous 1 mg E<sub>2</sub>, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 ug NGM, and 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 ug NGM groups at 7 and 12 months, and at Month 12 for the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 ug NGM group. HDL<sub>2</sub>-Cholesterol was increased for all four groups at both Months 7 and 12. Triglycerides increased less during treatment with the cyclophasic groups than with the continuous E<sub>2</sub> group. Increases in Sex Hormone Binding Globulin (SHBG) were smaller with the 1/1+90 and 1/1+180 groups (see Table 16).

Table 16: Lipids, Triglycerides, and SHBG Mean Percent Changes from Baseline to Months 7 and 12

Lipid Parameter (mg/dl)	1 mg E <sub>2</sub> (N) Mean % change	1 mg E <sub>2</sub> /30 µg NGM (N) Mean % change	1 mg E <sub>2</sub> /90 µg NGM (N) Mean % change	1 mg E <sub>2</sub> /180 µg NGM (N) Mean % change
Total Cholesterol				
Month 7	(52) -1.6	(48) -3.7	(44) -6.2	(49) -5.3
Month 12	(36) 1.2	(39) -0.5	(31) -1.9	(39) -2.7
HDL-Cholesterol				
Month 7	(52) 9.4	(47) 6.6	(43) 3.6	(48) -3.9
Month 12	(36) 12.0	(39) 8.7	(31) 9.7	(39) 6.1
HDL <sub>2</sub>				
Month 7	(52) 42.4	(47) 53.1	(43) 20.6	(46) 18.0
Month 12	(36) 75.3	(39) 26.7	(31) 28.9	(38) 31.6
LDL Cholesterol				
Month 7	(45) 4.4	(42) -5.5	(39) -4.2	(44) 1.1
Month 12	(31) 1.7	(34) -0.7	(30) 1.2	(36) 6.0
Triglycerides				
Month 7	(52) 20.8	(48) 16.8	(44) 8.8	(49) 12.3
Month 12	(36) 29.0	(39) 22.9	(31) 9.4	(39) 0.7
SHBG (nmol/L)				
Month 7	(49) 111.9	(45) 175.7	(41) 57.7	(45) 41.6
Month 12	(32) 98.8	(35) 194.0	(29) 67.8	(36) 39.5

Source: NDA 21-040, Item 8, Volume 32, page 108

No clinically relevant changes were noted in mean percent changes from baseline in fasting glucose or fasting insulin concentrations, or in blood coagulability parameters in any of the 1 mg E<sub>2</sub> treatment groups.

#### 5.13 Summary of DSI audit

Four DSI audits were completed, two for Study 102 and two for Study 103. For Study 102, DSI audits were completed at the sites. Per the Division of Scientific Investigations, Clinical Investigations Branch, the site was issued, at the close of the inspection, a Form FDA 483 which listed the following:

DSI noted comments received from the site in response to the above observations. The site was also issued a Form 483, which listed the inspector's observation regarding drug accountability records. A letter, dated 4/5/99, in reply to this issue was acceptable.

For Study 103, DSI audits were completed at the sites. Both sites did adhere to all federal regulations and/or good clinical investigational practices governing conduct of clinical investigations and the protection of human subjects.

#### 6. Supportive Clinical Trials: N93-072, CC2636-C-101, and ESTNRG-CHRT-105

##### Study N93-072

This was the first study undertaken in the US to evaluate Ortho-Prefest™. Study N93-072 was a 12 month, double-blind, parallel-group, multicenter (19 in the US and 1 in Costa Rica), dose-ranging study in which 414 postmenopausal women (≥ 12 months), aged 40-65 years, with intact uteri and baseline FSH > 40 mIU/ml and estradiol ≤ 20 pg/ml were randomized to receive one of eight treatment regimens (four 1 mg E<sub>2</sub> groups [E<sub>2</sub> alone and with 30, 90, and 180 µg NGM] and four similar 2 mg E<sub>2</sub> groups) to evaluate efficacy in preventing endometrial hyperplasia and to secondarily assess vaginal bleeding, changes in vaginal cytology, and improvement in vasomotor symptoms.

The design of Study N93-072 included a two-month "priming" phase that preceded the 12-month treatment phase (E<sub>2</sub> alone given on days 1-42, cyclophasic regimen given on days 43-54, placebo given on days 55-60). Per the sponsor, the purpose of the priming phase was to produce an estrogen-stimulated endometrium and then compare the progestational potencies of three different doses of

NGM added sequentially to estrogen treatment. The 12-month treatment phase began on day 61. Endometrial biopsies were obtained pretreatment, during days 49-54 of the priming phase, and during the last five days of treatment in month 12. Transvaginal ultrasonography and vaginal smears for maturation index were completed pretreatment, days 49-54 of the priming-phase, Month 7, and at the end of Month 12.

An interim analysis was planned to analyze the frequency, severity, and pattern of vaginal bleeding in each treatment group when approximately 30 subjects per group had completed six months of treatment. The purpose of the interim analysis was to allow dose selection for future HRT studies.

Hyperplasia (a total of 45 cases based on the efficacy reading, including one case of adenocarcinoma) at Month 12 (or earlier in the treatment phase) occurred in six of the eight treatment arms. Only the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM regimens remained free of hyperplasia.

The incidence of bleeding or spotting (based on subjects with 12 months of treatment data) was lower in each of the 1 mg E<sub>2</sub> groups than in the corresponding (same amount of NGM) 2 mg E<sub>2</sub> groups, with the least favorable results in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+90 µg NGM (69.2%, 18 of 26 subjects) and 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM (78.6%, 22 of 28 subjects) groups. Statistical comparisons between treatment groups, for the mean number of days per month with bleeding and spotting during the treatment phase, showed that the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM group had the lowest mean number of days (2.2 days) and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM group had the highest (10.7 days).

Changes in vaginal cytology during treatment appeared similar in all treatment groups as shown by decreases in parabasal cells and increases in intermediate and superficial cells. Parabasal cells (ranging from 29% to 56% of the epithelial cell count at pretreatment) decreased to ≤ 3% in each treatment group by the end of priming and remained at low levels for the duration of treatment (0.0% to 3.4% at 12 months). Superficial cells (2.9% to 7.2% of epithelial cells at pretreatment) increased to a range of 21.4% to 32% at 12 months.

No deaths occurred during the study. Across treatment group, adverse events reported by the greatest percentage of subjects were headaches, back pain, dysmenorrhea, abdominal pain, and sinusitis. The most significant adverse event with an incidence of ≥ 5% was endometrial hyperplasia (safety reading).

Malignant neoplasm documented during the study in the 2 mg E<sub>2</sub> groups included one each: breast cancer (2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+30 µg NGM, considered as unlikely relationship to study drug as pretreatment mammogram showed possible focal distortion without associated mass), endometrial adenocarcinoma (2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+90 µg NGM, certain relationship to study drug), thyroid neoplasm (2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+90 µg NGM, considered unlikely relationship to study drug), and colon cancer (relationship to 2 mg E<sub>2</sub> alone considered unlikely).

One report of cholecystitis with subsequent cholecystectomy in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+30 µg NGM group occurred 16 weeks after completion of the study and was evaluated as having an unlikely relationship to the study therapy.

#### Reviewer's comments

The absence of a washout period for prior sex hormone use (as suggested in the HRT Guidance for Industry) and the inclusion of a "priming" phase in this protocol complicates interpretation of results. Nonetheless, results demonstrate (after 12 months of treatment) the absence of hyperplasia in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM groups, an increased incidence of bleeding and spotting in all the 2 mg E<sub>2</sub> groups, and less favorable bleeding result in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+180 µg NGM group compared to the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group early in the treatment period.

Based on these results the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM regimen appears to be the lowest progestin dose necessary to protect the endometrium exposed to continuous 1 mg E<sub>2</sub>, and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM regimen has the more favorable bleeding patterns.

Per the sponsor, improvement in the rate of hot flushes occurred largely during the priming phase. Results of the effect of the cyclophasic regimens on vasomotor symptoms were not presented.

#### Study CC2636-C-101

Study C-101 was a 12-month, parallel-group, multicenter (42 centers in Belgium, Finland, Sweden, and The Netherlands) study in which 657 postmenopausal women (≥ 12 months), aged 40-65 years, with intact uteri and baseline FSH > 40 mIU/ml and estradiol ≤ 20 pg/ml were randomized to receive one of three treatments (1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM [cyclophasic-low], 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM [cyclophasic-high], or 2 mg E<sub>2</sub>/1 mg norethindrone acetate [Kliogest®]) to determine uterine bleeding patterns and the effect on endometrial histology, and to evaluate changes in the frequency of vasomotor symptoms and safety by standard safety parameters and serum lipids.

Subjects completed diary cards with information on bleeding, vasomotor symptoms and pill intake. Endometrial biopsies were taken prior to and at the end of treatment, after 6 months if the endometrial thickness was ≥ 5mm, or when deemed indicated. A washout period from prior hormone use was observed which did not meet the Agency's HRT Guidance (the protocol excluded transdermal use within 2 weeks of screening and within 4-6 weeks for oral products). Subject inclusion did not require either a baseline number of hot flushes or a moderate-to-severe classification of severity.

An interim analysis was conducted on data of the first 300 subjects completing 6 months of treatment in order to examine uterine bleeding and discontinuation. Moderate and severe uterine bleeding was reported by 29% of subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group (n=221) and 25% in the Kliogest® group (n=217). Sixty-nine percent (69%) of subjects in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group (n=219) reported moderate or severe uterine bleeding. Around 15% of subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group and the Kliogest® group withdrew prior to completion of 6 months. In the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group, the proportion was higher, 44.4%.

Slightly more than one half of subjects experienced bleeding at some time during the first six months of treatment for cyclophasic-low and Kliogest®, 56% and 51%, respectively. The difference in the results is not statistically significant, however (p=0.388). In contrast, 84% of subjects on the cyclophasic-high regimen experienced bleeding in the first six months. This difference, relative to the reference regimen, is statistically different in favor of Kliogest® (p<0.001).

During Months 7-12, the number of subjects experiencing bleeding was lower, for all three regimens, than during the first 6 months. The reduction was most prominent in the Kliogest® group by nearly one half, from 51% in the first 6 months to 29% in the last 6 months of the study. The reduction was less prominent, yet similar, for the cyclophasic-low and cyclophasic-high groups (55% to 45% and 84% to 74%, respectively). The differences compared to Kliogest® are both statistically significant in favor of the reference treatment (p<0.002 for cyclophasic-low and p<0.001 for cyclophasic-high).

Overall, uterine bleeding (from adverse events and 'other') was the predominant reason for withdrawal from the study and led to 34% withdrawal in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group (75 of 219 subjects), compared to 8% in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group (18 of 221) and 9% in the Kliogest® group (19 of 217).

Histological analysis of biopsies revealed no case of hyperplasia or cancer either at Month 7 or at the end of treatment in any treatment group. However, twenty-four (4.4%) of final biopsy specimens were diagnosed as insufficient tissue. The estimate for hyperplasia/cancer incidence from baseline to end-of-treatment is zero in all groups. The confidence intervals range from zero to 1.95 for cyclophasic-low, 0-2.07 for cyclophasic-high, and 0-2.00 for Kliogest®.

No baseline hot flush frequency and severity inclusion criteria were observed. Subjects kept diary card information for 30 days prior to treatment that provided the baseline number/severity data. The mean number of hot flushes per day during baseline and during the last 30 days of treatment was analyzed. At baseline the mean number of hot flushes ranged from 5.0 to 5.4 (SD=4.43 to 5.16). Per the sponsor, by Week 8, a reduction of > 90% was observed in all treatment groups. At the end of the study, the average reduction in the mean number of hot flushes was between 93% and 95% in all treatment groups (NDA 21-040, Item 8, Volume 157, pages 61-62).

No laboratory values of note were identified except for: 1) an increase in HDL-C, and specifically HDL<sub>2</sub>-C, in the cyclophasic regimens compared to Kliogest® (median % change of 20.37 for cyclophasic-low [CI=13.95-26.67] and 7.17 for cyclophasic-high [CI=3.45-12.12] versus -6.69 for Kliogest® [CI=-10.53 to -3.28]); and 2) three subjects in the cyclophasic-high group experienced anemia.

No subjects died during the study. One subject (Subject 103) had a diagnosis of pulmonary cancer and died 71 days after withdrawal from the trial (1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group, considered to be unlikely related to regimen). One breast carcinoma was observed in the cyclophasic-high (2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM,) treatment group (considered to be probably related to study medication). One subject experienced obstructive icterus caused by cholelithiasis and cholecystitis and underwent a cholecystectomy (2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM, considered to be possibly related to the study medication). Across treatment group, adverse events reported by the greatest percentage of subjects were vaginal bleeding; headaches; breast, back, and abdominal pain; nausea; viral infection and influenza-like symptoms; and dysmenorrhea.

#### Reviewer's comments

Based on evaluable biopsies, both doses of cyclophasic NGM (90 and 180 µg) protected the endometrium. The data presented also clearly demonstrates a higher incidence of uterine bleeding in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group while the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM and the Kliogest® groups produced similar uterine bleeding patterns for the first 6 study months. However, bleeding decreased less in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group than the Kliogest® group during the last 6 months of the study.

The washout periods observed in this protocol did not meet the suggested washout periods for a relief of vasomotor symptoms indication as stated in the Agency's HRT Guidance. In addition, this protocol did not seek to enroll postmenopausal women with at least 7-8 moderate-to-severe hot flushes per day or at least 60 per week at baseline. Due to these deficiencies, the data presented for relief of vasomotor symptoms has limited value.

#### Study ESTNRG-CHRT-105

ESTNRG-CHRT-105 was an extension of Protocol CC2636-C-101 and subjects completing C-101 could be enrolled in this study for a second year of treatment with the same therapy. Four hundred and eight (408) of the eligible 471 subjects completing C-101 participated in Study 105. Subjects continued to record daily pill intake, vaginal bleeding and hot flushes. An endometrial biopsy was obtained at 24 months or sooner, as needed.

The overall rate of bleeding was similar in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group (61%, 91 of 150 subjects) and the Kliogest® reference group (60% 103 of 172 subjects), but was higher in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group (80%, 69 of 86 subjects). When spotting only was reported, the overall incidence was similar in the two cyclophasic groups (23 [15%] of 150 in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group and 14 [16%] of 86 in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group), and less than that reported in the Kliogest® reference group (34 [20%] of 172 subjects).

The percent of subjects who experienced no bleeding or spotting increased over time. For the 150 subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group, 57% (86 of 150) reported no bleeding or spotting at month 1 and 73 % reported no bleeding or spotting at month 24 (99 of 150). However, no consistent increase was seen in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group (41% [35 of 86] at month 1 and 40% [34 of 86] at month 24). In contrast, 58% of the reference group (99 of 172) reported no bleeding or spotting at month 1 compared with 83% (133 of 172) reporting no bleeding and spotting at month 24.

An endometrial biopsy was obtained at 24 months in 83% (n=125) of the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group, 87% (n=75) of the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group, and 91% (n=157) of the Kliogest® reference group. Twenty (4.7%) of these final biopsy specimens were diagnoses as insufficient tissue. In the remaining evaluable biopsies, no cases of hyperplasia or cancer occurred in any of the treatment groups. The observed incidence of hyperplasia, therefore, is zero with all three treatment groups.

At the start of the extension year the mean number of hot flushes at baseline for the three treatment groups ranged from 5.0 to 5.7 (SD=4.35 to 5.16). The mean change from baseline to study end ranged from -4.9 to -5.5 (SD=4.01-5.08) with a mean percent change from baseline, for the three treatment groups of 95.5%.

Uterine bleeding was reported as an adverse event in a higher proportion of subjects in the cyclophasic-high group (21%, 18 of 86 subjects), than in the cyclophasic-low group (15%, 22 of 150) or the Kliogest® reference group (12%, 21 of 172). Overall, the most common adverse events were headache, influenza-like symptoms, breast pain, back pain, and uterine bleeding which occurred in similar proportions of subjects in the three treatment groups, except for the rate of breast pain which was higher in the reference group (26% versus 13% and 17% in the cyclophasic groups).

No laboratory values of note were identified except for an increase in HDL<sub>2</sub>-C in the cyclophasic regimens compared to Kliogest® (mean % change from baseline of 13.4% for cyclophasic-low [mean=0.61, SD=0.203] and 11.1% for cyclophasic-high [mean=0.60, SD=0.204] versus -14.0% for Kliogest® [mean=0.46, SD=0.162]). LDL-Cholesterol levels decreased in all treatment groups with a slightly smaller percent change in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group (-16.3% in the reference group, -14.5% in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group, and -11.2% in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub>+90 µg NGM group).

No deaths occurred during the study. One subject (Number 628) developed breast cancer (cyclophasic-high group, Study Day 732) which the investigator considered unlikely related to study medication. One subject (Number 593) with no history of cardiovascular problems, randomized to the reference group, developed a myocardial infarction (Study Day 663) that the investigator considered unlikely related to study medication. Subject Number 48 developed non-Hodgkins lymphoma (Study Day 571) which the investigator considered possibly related to study medication.

#### Reviewer's comments

In this additional 12-month study, uterine bleeding continued to be more common in the 2 mg E<sub>2</sub>/2 mg E<sub>2</sub>+180 µg NGM group. As stated previously for Study 101, the data presented for relief of vasomotor symptoms has limited value.

Adverse events reported may be considered expected. Based on evaluable biopsies, all three treatment groups protected the endometrium.

#### 7. Labeling review

The sponsor submitted a revised label in four amendments to the NDA, dated September 2, 1999, October 15, 1999, October 20, 1999, and October 22, 1999. The following labeling changes incorporate those proposed for the revised Physician's Package Insert submitted on September 2, 1999, October 15, 1999, October 20, 1999, and October 22, 1999; and for the revised Patient Package Insert

submitted October 15, 1999 and October 20, 1999. The page numbers given refer to the final labeling dated October 22, 1999.

Physician's Package Insert

Redacted

4

pages of trade

secret and/or

confidential

commercial

information

8. Reviewer's assessment of efficacy and safety

Oral estrogen replacement therapy is known to be effective in the treatment of vasomotor symptoms and the prevention of osteoporosis. However, the long-term use of unopposed estrogen is associated with an increased incidence of endometrial hyperplasia in menopausal women with uteri. The addition of a progestin to estrogen therapy (added for 10-14 days per month) reduces the risks of endometrial hyperplasia.

Ortho-Prefest™ is a product proposed for hormone replacement therapy that provides interrupted progestin treatment during continuous estradiol treatment. Three days of estradiol alone treatment is followed by three days of estradiol plus norgestimate treatment. This regimen is repeated continuously. This interrupted method of progestin administration, first proposed by Upmalis and Casper in 1991, is based on animal and human studies showing that progestin caused down-regulation of endometrial estrogen and progesterone receptors while estrogen up-regulates both type of receptors. Therefore, receptor levels that decrease during estrogen/progestin treatment will recover during the subsequent period of estrogen-only administration. The sponsor hypothesizes that giving progestin in a 3-days-on and 3-days-off schedule, with continuous estrogen, will allow receptor levels decreased during the days of combination treatment to recover during the subsequent period of estrogen-only treatment. This "recovery" would result in an increase in the concentration of progestin receptors thereby allowing for the use of a lower dose of progestin to achieve the desired progestational effect.

In this NDA, three proposed indications were submitted: treatment of moderate-to-severe vasomotor symptoms, treatment of vulvovaginal atrophy, and the prevention of osteoporosis. Clinical data was presented for relief of vasomotor symptoms and vulvovaginal atrophy, and protection of the endometrium. In two single-dose bioequivalent studies the 0.5 mg and 2 mg E<sub>2</sub> tablets were found to be bioequivalent to the 0.5 mg and 2 mg Estrace® estradiol tablets. No clinical data was submitted for the prevention of osteoporosis indication.

NDA 21-040 presents data from six clinical trials to support the efficacy and safety of Ortho-Prefest™. These include one pivotal 12-week, Phase 3, placebo-controlled study (ESTNRG-CHRT-104) with estradiol alone (0.5 and 1 mg), conducted to evaluate the efficacy and safety of two doses of estradiol for relief of vasomotor symptoms; and two pivotal, 12-month, Phase 3 studies (ESTNRG-CHRT-102 and 103) conducted to evaluate the efficacy and safety of five different estradiol and norgestimate cyclophasic regimens (3 different 1 mg E<sub>2</sub> regimens, and 2 different 2 mg E<sub>2</sub> regimens) compared to two doses of continuous estradiol alone (1 and 2 mg) for the effect on endometrial histology, vaginal bleeding, vasomotor symptoms, vulvovaginal atrophy, and metabolic and coagulation variables (Study 102 only). Data from these two 12-month studies were pooled, per agreement of the Division. All three of these Phase 3 studies were conducted in the US under IND

In addition, three supportive studies were submitted. Study N93-072, also conducted in the US under IND was a Phase 2, 12-month, double-blind, dose-ranging study (including six different estradiol and norgestimate cyclophasic regimens and two doses of continuous estradiol alone) conducted to evaluate efficacy and safety in preventing hyperplasia.

Study CC2636-C-101 and Study ESTNRG-CHRT-105 were non-IND studies conducted in Europe. Study 105 was an extension of Study 101. Both studies were 12-month, parallel group studies that compared two different estradiol and norgestimate cyclophasic regimens to a reference product, Kliogest™, to determine uterine bleeding patterns and the effect on endometrial histology.

These three studies are considered supportive because tablets used in these studies were manufactured by a wet granulation process that differed from the dry blend process used in the pivotal studies and proposed for marketing. Per the sponsor, the wet granulation process tablets produced 35% higher C<sub>max</sub> values for E<sub>2</sub> and NGM than the dry blend tablets. However, systemic exposure as measured by AUC was similar for both formulations.

When the results of the interim analysis of bleeding in Study N93-072 revealed unfavorable bleeding results for the 2 mg E<sub>2</sub> regimens, the sponsor discontinued currently-enrolled subjects receiving the 2 mg E<sub>2</sub> regimens in the Phase 3 studies and discontinued randomization of subjects to these regimens.

#### Treatment of moderate-to-severe vasomotor symptoms

Based on the ANOVA analysis of Randomization 2 in the pivotal double-blind, 12 week Study 104 (1 mg E<sub>2</sub> versus 0.5 mg E<sub>2</sub> versus placebo), the mean change from baseline in the number of moderate or severe hot flushes was statistically and clinically significant between the 1 mg E<sub>2</sub> group and the placebo group at Week 4 (p<0.001) which was sustained through Week 12 (p<0.001). The difference between the 0.5 mg E<sub>2</sub> group and the placebo group for moderate-to-severe hot flushes was also statistically and clinically significant, beginning at Week 8 (p=0.006) through Week 12 (p=0.006). Although no statistical dose-response analysis between the E<sub>2</sub> groups was performed, the results appear consistent with a dose response. The difference between active treatment and placebo in the mean number of hot flushes began significantly earlier with the 1 mg E<sub>2</sub> dose than with the 0.5 mg E<sub>2</sub> dose.

No placebo-controlled data was submitted for the treatment of moderate-to-severe vasomotor symptoms with the cyclophasic HRT regimens. Studies 102/103 (1 mg E<sub>2</sub> alone versus 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM, 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM, and 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM) were not designed to evaluate vasomotor symptoms as a primary end-point, and in fact, did not observe inclusion criteria for baseline number and severity of hot flushes. Subjects with and without hot flushes at baseline were enrolled. However, study participants did keep daily hot flush number and severity data on diary cards for the first 12 weeks of these 12-month studies.

Diary card data for hot flushes (any number at baseline, and all severity classifications) and for moderate-to-severe hot flushes (any number at baseline, not 7-8 per day at baseline per the HRT Guidance) was analyzed by the sponsor and reported for baseline and 4, 8, and 12 weeks of treatment. The results of the prospective analysis of moderate-to-severe hot flushes in Studies 102/103 are included in Section 5.11, Efficacy Analysis, of this review. The results show similar mean changes in hot flushes between the four 1 mg E<sub>2</sub> treatment groups. As compared to the continuous 1 mg E<sub>2</sub> group,

the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen produced a similar mean change in the average number of moderate-to-severe hot flushes at Week 12 (mean change of -2.0 [SD=3.72] for the 1 mg E<sub>2</sub> group compared to a mean change of -2.0 [SD=3.24] for the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen).

On June 10, 1999, the Division received requested post-hoc analysis data from the sponsor demonstrating the mean change in the mean daily number of moderate-to-severe hot flushes during therapy for study participants with ≥ 7 moderate-to-severe hot flushes per day at baseline. Later, on August 5, 1999, requested post-hoc analysis data was received showing the change in the mean daily number of moderate-to-severe hot flushes for all subjects in the four 1 mg E<sub>2</sub> groups with ≥ 7 moderate-to-severe hot flushes per day at baseline. Between 8.6% and 12% of subjects (across the four treatment groups, ranging from 26-37 subjects per group) reporting vasomotor symptoms at baseline met this criteria. The post hoc analysis of this subgroup population demonstrates that the magnitude of mean change in moderate-to-severe hot flushes over 4, 8, and 12 study weeks was similar in each group. Only the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM dose was statistically significant at Week 12 (p=0.003). Otherwise, there were no statistically significant differences between groups. The overall results of this post-hoc analysis of a subgroup population in Studies 102/103 provides supportive evidence that concomitant norgestimate treatment (i.e., the Ortho-Prefest™ regimen) produces a similar reduction in the mean daily number of moderate-to-severe hot flushes at Week 4 sustained through Week 12 as does continuous 1 mg E<sub>2</sub> in Study 104.

Based on the data submitted in this NDA for the relief of moderate-to-severe vasomotor symptoms for the proposed to-be-marketed 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen, there is limited prospective clinical data to support approval. The two 12-month pivotal clinical trials with the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM Ortho-Prefest™ regimen were insufficient in design to support an indication for the relief of vasomotor symptoms. The subgroup data provides supportive evidence, however, that intermittent norgestimate, given with continuous E<sub>2</sub>, does not reduce the efficacy of estradiol in relieving moderate-to-severe vasomotor symptoms associated with the menopause. The critical link for support of the efficacy of Ortho-Prefest™ in relieving moderate-to-severe vasomotor symptoms is based on pharmacokinetic (PK) data.

Single dose PK studies demonstrate bioequivalence of the sponsor's E<sub>2</sub> to Estrace®. A multiple dose PK study suggests that the steady state E<sub>2</sub> level following administration of the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen is approximately 12% - 18% below the steady state E<sub>2</sub> level obtained following the administration of continuous 1 mg E<sub>2</sub> alone. Therefore, the efficacy of the Ortho-Prefest™ regimen could be reduced in those days when the E<sub>2</sub> plus norgestimate is given compared to those days in which E<sub>2</sub> alone is administered. Consideration of these findings should be addressed in labeling for the relief of vasomotor symptoms indication.

#### Treatment of vulvovaginal atrophy

Vaginal epithelial cytology (the maturation index) was evaluated in Study 104, Study 102, and in Study N93-072. In Study 104, the two doses of continuous estradiol (0.5 and 1 mg) were similarly effective in increasing the proportion of superficial vaginal cells and statistically superior to placebo (p=0.004 for 0.5 mg E<sub>2</sub> and p=0.001 for 1 mg E<sub>2</sub>).

All of the 1 mg E<sub>2</sub> cyclophasic HRT regimens in Study 102 and Study N93-072 had similar effects on vaginal epithelial cytology, as shown by a "shift to the right," i.e., an increase in superficial cells and a decrease in parabasal cells. The mean change from baseline in the maturation index suggests a dose response in the three cyclophasic regimens, but no statistically significant differences between continuous E<sub>2</sub> and any of the cyclophasic groups were found.

No data was submitted for a 0.5 mg E<sub>2</sub> cyclophasic HRT regimen. Therefore, it is not possible to conclude that the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen is the lowest dose for vulvar and vaginal atrophy given the efficacy of the 0.5 mg E<sub>2</sub> alone results. Labeling should reflect that the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM dose may not be the lowest effective dose for the treatment of vulvar and vaginal atrophy.

#### Protection of the endometrium

Endometrial histology at 12 months was evaluated in Studies 102/103 and Study C-101. Study 105 evaluated endometrial histology at 24 months. Study N93-072 also evaluated endometrial histology pretreatment and after 12 months of study medication. However, the 2-month priming phase included in this protocol complicates the interpretation of the results.

In Studies 102/103, no cases of endometrial hyperplasia were diagnosed in final efficacy biopsy results (Intent-to-Treat population) for the 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM or the 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180 µg NGM regimens. Whereas, the incidence of hyperplasia was 29% in the 1mg E<sub>2</sub> alone group and 6.5% in the 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM group. Differences between groups were highly significant (p<0.001) confirming the dose-related efficacy of norgestimate in preventing endometrial hyperplasia. However, 56 of the 1010 subjects (5.5%) in the Intent-to-Treat population had insufficient tissue obtained for diagnosis. It is not possible to know the histology results for these subjects.

The efficacy histology results obtained at the end of treatment in supportive Study C-101 (12 months) and Study 105 (24 months) revealed no cases of hyperplasia in any treatment group. In these studies, however, only two pathologists examined the biopsy slides. Similar to Studies 102/103, insufficient tissue results were observed in 4.3% of biopsies in Study C-101 and in 5% of biopsies in Study 105. No definitive diagnosis could be reached for these subjects.

Overall, the data submitted with this NDA support the conclusion that the 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen is the lowest norgestimate dose which adequately protects the endometrium.

#### Prevention of Osteoporosis

No clinical trials were conducted to assess the bioequivalence of the 1 mg E<sub>2</sub>/ 1 mg E<sub>2</sub> + 90 µg NGM regimen for the prevention of osteoporosis. However, in two single-dose bioequivalent studies the 0.5 mg and 2 mg E<sub>2</sub> tablets were found to be bioequivalent to the 0.5 mg and 2 mg Estrace® (estradiol) Tablets. Additionally, the formulation of the 1 mg E<sub>2</sub> tablet is proportionally similar to the formulations of the 0.5 mg E<sub>2</sub> and 2 mg E<sub>2</sub> tablets, and the dissolution profile is similar to the dissolution profiles for the 0.5 mg E<sub>2</sub> and the 2 mg E<sub>2</sub> tablets. Therefore, a bioequivalence study waiver is granted for the 1 mg E<sub>2</sub> tablet (to the 1 mg Estrace® Tablet).

The 0.5 mg dose of Estrace® is the lowest effective dose for the prevention of osteoporosis. The Ortho-Prefest™ labeling should reflect that the 1 mg E<sub>2</sub>/ 1 mg E<sub>2</sub> + 90 µg NGM regimen may not be the lowest effective dose for the prevention of osteoporosis.

#### Safety Assessment

The principal safety data were derived from the completed Phase 2 and Phase 3 cyclophasic HRT (12 months) and E<sub>2</sub> only (12 weeks) studies. In these studies, 2908 subjects were evaluated for safety, including 408 subjects who received up to two years of treatment. Overall, 579 subjects received up to one year and 150 subjects received up to two years of treatment with the 1 mg E<sub>2</sub>/ 1 mg E<sub>2</sub> + 90 µg NGM regimen, for a total of 481.2 and 278.2 subject-years, respectively. The population of subjects in the completed Phase 2 or 3 studies was comprised predominantly of white postmenopausal women (89%) who had a median age of 54 years. The majority of subjects (65%) had experienced their last menses more than three years prior to study entry.

Fifty-six percent (56%) of the 1-year safety group (Studies N93-072, C-101, 102/103) completed the studies. Subjects in the 2 mg E<sub>2</sub> groups comprised the largest study population withdrawn from treatment. This was primarily due to a protocol amendment of Studies 102/103, when Study N93-072 showed relatively unfavorable bleeding patterns in these study groups. Discontinuation rates due to adverse events were lower among the three cyclophasic HRT regimens (6-8%) compared with continuous 1 mg E<sub>2</sub> (16%). In Studies 102/103 (including the 1 and 2 mg E<sub>2</sub> groups), vaginal bleeding (either recorded as an adverse event or classified as "other" reason for withdrawal) and endometrial hyperplasia were the most frequently reported treatment-limiting adverse events.

The 2-year safety group consisted of 408 subjects who completed Study C-101 and extended for one additional year (Study 105). Ninety percent of subjects completed the second year of HRT.

One subject died receiving study treatment during the six completed Phase 2 and 3 studies. Two subjects died after discontinuation of study medication. A full report of these deaths can be found on pages 26 and 33 of this review. These deaths appear to have an unlikely relationship to study medication.

The incidence of frequently reported adverse events (i.e., those reported by  $\geq 5\%$  of subjects) in the individual pivotal and supportive studies submitted in this NDA have been summarized previously in this review. Excluding endometrial hyperplasia, the most frequently reported adverse event, by preferred term, for the total study populations in the 1-year safety group (2,908 subjects in Studies N93-072, C-101, and 102/103) include: headache (20%), breast pain (19%), upper respiratory tract infection (19%), abdominal pain (13%), dysmenorrhea (12%), and all vaginal bleeding (11%).

The most common reported adverse events, by preferred term, for subjects in the 2-year safety group of Studies C-101/105 included headache (32%), influenza-like symptoms (26%), breast pain (19%), back pain (16%), vaginal bleeding (16%), and abdominal pain (15%).

These reported adverse events may be considered expected, and are generally similar to adverse events known to occur during treatment with estrogens and/or progestins.

Among the reports of non-fatal serious adverse events were eight cases of breast cancer diagnosed during study treatment. Four cases of breast cancer were diagnosed in the 2 mg E<sub>2</sub> groups, and four cases were diagnosed in the 1 mg E<sub>2</sub> groups. Three of the cases in the 1 mg E<sub>2</sub> groups were evenly divided among the three cyclophasic groups. One subject, in the 1 mg E<sub>2</sub> alone group, was diagnosed with a breast neoplasm that was a borderline lesion between atypical intraductal hyperplasia and cribriform intraductal carcinoma. Overall, these results do not indicate a higher incidence of breast cancer than reported for other large HRT clinical trials.

There were a total of eleven reports of cholelithiasis or cholecystitis (nine in Studies 102/103, one in Study N93-072 and one in Study C-101). They occurred in three of the four 1 mg E<sub>2</sub> groups (no cases were reported for the 1 mg E<sub>2</sub>/180  $\mu$ g NGM group), and in two of the three 2 mg E<sub>2</sub> groups (no cases were reported for the 2 mg E<sub>2</sub>/180  $\mu$ g group). Of concern is the imbalance in the number of reported cases of cholelithiasis or cholecystitis and the number of cholecystectomies among the seven treatment groups. Of the eleven reports of cholelithiasis or cholecystitis, five cases occurred in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90  $\mu$ g NGM group and four of these five subjects had cholecystectomies. While these numbers do not indicate a higher incidence of gallbladder disease and cholecystectomies with Ortho-Prefest™ than reported in other large clinical trials, they warrant close post-marketing surveillance.

Based on the efficacy reading of endometrial biopsies in Studies 102/103, there were no cases of endometrial hyperplasia among subjects who received the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90  $\mu$ g NGM and the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 180  $\mu$ g NGM regimens. In these studies, endometrial hyperplasia diagnosed during the safety (initial) readings of biopsies was reported as adverse events. Safety readings were the readings immediately available to the investigators, and they served as the basis for the clinical management of the study subjects. A single, central laboratory provided the safety readings with multiple pathologists participating. Safety readings were the only biopsy readings performed for the 2 mg E<sub>2</sub> groups in Studies 102/103 after discontinuation of those treatment groups. Results of the safety readings of endometrial biopsies for Studies 102/103 are shown on the following page:

Continuous 1 mg E <sub>2</sub> (n = 311) 83 (27%)	Cyclophasic 1/30 (n = 312) 30 (10%)	Cyclophasic 1/90 (n = 312) 3 (1%)	Cyclophasic 1/180 (n = 316) 2 (1%)
Continuous 2 mg E <sub>2</sub> (n = 207) 56 (27%)	Cyclophasic 2/90 (n = 213) 1 (<1%)	Cyclophasic 2/180 (n = 202) 0 (0%)	

There is a discrepancy in the incidence of endometrial hyperplasia in the safety readings and the efficacy reading of endometrial biopsies for the to-be-marketed 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen. The safety readings for Studies 102/103 gave higher incidences of hyperplasia, for all the 1 mg E<sub>2</sub> groups, than did the efficacy readings. Inter-observer variability (multiple pathologists) can account for a certain number of observed discrepancies. However, the efficacy readings which were conducted by the same two, independent and blinded, pathologists with a third, independent and blinded, pathologist acting as arbitrator, are considered definitive as the evaluation procedure employed complied with the 1995 HRT Guidance requirements for an endometrial protection indication.

The effects of race, age, and body weight on the pharmacokinetics of E<sub>2</sub> and norgestimate and their metabolites were evaluated in five single-dose pharmacokinetic studies (PHI-002, 004, 006, 007, and 008). No significant pharmacokinetic difference was found regarding race and age in the pharmacokinetics of E<sub>2</sub> or E<sub>2</sub> or NGM metabolites (E<sub>1</sub>, E<sub>1</sub>S and 17d-NGM, NG, respectively). However, women who weighed >80 kg had peak serum 17d-NGM concentrations that were approximately 40% lower, 30% lower AUC values for 17d-NGM, and peak serum NG concentrations that were approximately 30% lower than women in the <60 kg and 60-80 kg weight groups. Two hundred and fifty subjects (15.1%) in the overall 1 mg E<sub>2</sub> study population (n=1656) had a body weight over 80 kg. Overall, the incidence of adverse events for some body systems including -body as a whole, general disorders, respiratory system disorders, and gastrointestinal systems disorders, tended to be higher in the higher weight subjects in some, but not all, of the treatment groups. Likewise, the incidence of reproductive disorders adverse events, including endometrial hyperplasia, vaginal bleeding, breast pain and dysmenorrhea, tended to increase with subject weight (5% among subjects weighing <60 kg, 7% in the 60-80 weight group, and 12% in subjects >80 kg). This finding for endometrial hyperplasia, however, is based on the safety reading of endometrial biopsies and not the definitive efficacy reading. The definitive efficacy readings demonstrated no hyperplasia in the 1mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen.

In the completed Phase 2 and 3 studies, data revealed that the incidence of vaginal bleeding and spotting was higher with the 2 mg E<sub>2</sub> regimens than with the corresponding (same NGM dose) 1 mg E<sub>2</sub> regimens. The higher incidence of vaginal bleeding in the 2 mg E<sub>2</sub> groups, with subsequent increases in the incidence of withdrawals, primarily led to the discontinuation of the 2 mg treatment arms in ongoing studies. In Studies 102/103, the incidence of vaginal bleeding was highest in the continuous 2 mg E<sub>2</sub> group (15%) and lowest in both the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 30 µg NGM group and 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM groups (3%). Twenty-three percent (23%) of subjects in the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM group in Studies 102/103 were completely free of bleeding or spotting during all 12 months of treatment. The percentage rose to 51% at Month 12.

Overall, the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen produced a more acceptable bleeding profile.

#### Safety Updates

The Four Month Safety Update, dated April 23, 1999, covering the time period June 30, 1998 to February 19, 1999 includes information on two ongoing studies with Ortho-Prefest™

One death occurred in Study 106. A 64-year old subject who received study treatment (remains blinded) for 29 days was diagnosed with metastatic adenocarcinoma of unknown primary. While hospitalized, the subject experienced a pulmonary embolism with subsequent death. The investigator

evaluated the adenocarcinoma and pulmonary embolism as not related to the study therapy. Other serious adverse events in Study 106 (treatment remains blinded) include: benign cystic teratoma (72 days of treatment), poorly differentiated lung cancer (142 treatment days), breast cancer (180 treatment days), and multiple sclerosis (<180 treatment days). One serious adverse event was reported for Study 107. A 61-year old subject (Subject 61) was hospitalized and underwent surgery for varicose veins of the right leg, hemorrhoids, and anal polyps. Study therapy was not discontinued. One serious adverse event was reported for completed Study 103 submitted with this NDA. Two months after study completion Subject No. 75017 (49-year old) was diagnosed with a malignant melanoma, left elbow.

The Final Safety Update, dated September 24, 1999, covering the time period February 19, 1999 to August 6, 1999 includes information on three ongoing studies with Ortho-Prefest™

No additional deaths have been reported in these ongoing studies. One subject (Subject No. 9005 in Study randomized to placebo (blind broken on 2/19/99) was found to have simple hyperplasia and treated with MPA. One renal carcinoma (Subject 288 in Study was diagnosed on 4/15/99 and the subject continued on study medication (blind unbroken). No serious adverse events are reported for Study

Taken together, the results of the completed Phase 2 and 3 studies indicate that the overall adverse event profile observed with the 1 and 2 mg E<sub>2</sub> alone groups and the 1 and 2 mg cyclophasic HRT groups are consistent with that expected for estrogen only or estrogen/progestin regimens. Treatment for up to two years with the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM regimen appears safe and well tolerated by postmenopausal women.

9. Recommended regulatory action

The 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM Ortho-Prefest™ regimen is recommended for approval for the treatment of vasomotor symptoms, treatment of vulvar and vaginal atrophy, and the prevention of osteoporosis in postmenopausal women with a uterus.

Final labeling for the 1 mg E<sub>2</sub>/1 mg E<sub>2</sub> + 90 µg NGM Ortho-Prefest™ regimen is recommended for approval. On October 22, 1999, the Division received the sponsor's agreement to a Phase 4 commitment to revise the Patient Package Insert consistent with a plain language format.

/S/

10/22/99

Theresa H. van der Vlugt, M.D., M.P.H.  
Medical Officer

*J. Conner*

/S/

10/22/99

cc: NDA 21-040 Division File  
HFD-580/SSlaughter/DMoore/vanderVlugt

NDA 21-040

ORTHO-PREFEST (17 $\beta$ -estradiol and 17 $\beta$ -estradiol/norgestimate) tablets

R. W. Johnson Pharmaceutical Research Institute

**Safety Update Review**

The review of the safety update dated September 24, 1999, is found on page 45 in the Medical Officer's Review dated October 22, 1999.

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