CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-167

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW sNDA # 21167

July 7, 2000

1.1 DRUG NAME: Vivelle®, Estradiol Matrix Transdermal Therapeutic System

1.1.2 GENERIC NAME: Estradiol, Transdermal

1.1.3 PROPOSED TRADE NAME: Vivelle®

1.2 CHEMICAL FORMULA:

17β-estradiol; estra-1,3,5 (10)-triene-3, 17 β-diol; $C_{18}H_{24}O_2$; m.w. 272.39

1.3 SPONSOR: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

1.4 PHARMACOLOGICAL CATEGORY: estrogen, steroid hormone, transdermal delivery system

1.5 PROPOSED INDICATION: Prevention of postmenopausal bone loss. Efficacy is defined as changes in bone mineral density and biochemical markers of bone turnover.

1.6 DOSAGE FORM AND ROUTE OF ADMINISTRATION: Patches containing 4 dosages of estradiol for transdermal administration:

Dose Forms	Strengths (Nominal delivery)	Application Frequency
7.25 cm^2 patch	0.025 mg/day	Twice a week
11 cm^2 patch	0.0375 mg/day	Twice a week
14.5 cm^2 patch	0.05 mg/day	Twice a week
29 cm^2 patch	0.1 mg/day	Twice a week

1.7 NDA DRUG CLASSIFICATION: Estrogen; steroid hormone

1.8 IMPORTANT RELATED DRUGS: orally administered estrogen replacement dose preparations (e.g., Premarin® for relief of postmenopausal symptoms and for prevention of postmenopausal osteoporosis). Transdermal estrogen replacement dose preparations (e.g., Estraderm® , with nominal delivery rate of 0.05 mg and 0.1 mg/day) are currently approved for the treatment of postmenopausal vasomotor symptoms and prevention of postmenopausal osteoporosis.

1.8.1 FOREIGN MARKETING: Vivelle was approved in Canada in 1996 for relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states. Menorest™ estradiol transdermal system is identical to Vivelle and is marketed by Rhone Poulenc Rorer outside the U.S. and Canada for treatment of estrogen deficiency and postmenopausal osteoporosis.

1.9 RELATED REVIEWS:

a) Statistics
b) Chemistry
c) Biopharmaceutics
d) Pharmacology

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3 MATERIAL REVIEWED[1,2]: All clinical data in the electronic submission of NDA# 21-167, submitted October 19, 1999.

4 CHEMISTRY/MANUFACTURING CONTROLS: Per Chemistry review. According to Chemistry, there are no changes from cross-referenced NDA 20-323, in specifications, content/uniformity, impurities, formulation, or packaging. Stability data, which support the expiration dating period, are provided in the Vivelle annual report and are reviewed by Chemistry.

5 PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY: Per masterfile. The pre-clinical pharmacology/toxicology data have been reviewed as part of the original NDA. Additionally, biopharmaceutics and pharmacology reviews have been done because of the lower dose formulation.

5.1 Clinical pharmacology: Earlier studies in postmenopausal women (Study 1007, included in the Vivelle NDA 20-323) showed that steady-state blood levels of estradiol were dose-proportional in the range 0.0375-0.1mg/day. Pk data for the lower dose formulations of Menorest™ (0.025 and 0.037 mg), an identical transdermal product (Rhone Poulenc Rorer) have been published and are submitted with the present NDA. These data have been reviewed and confirm a dose-concentration linear relationship encompassing the 0.025mg/day dose.

6 CLINICAL BACKGROUND

Postmenopausal osteoporosis is a common disorder that is characterized by low bone mass and microscopic deterioration in bone architecture. In this condition, the quantity of bone is diminished, but the quality of the remaining skeletal tissue remains histologically normal, with no evidence of osteomalacia. The loss of bone mass and deterioration of bone microarchitecture results in increased bone fragility and susceptibility to fracture. In the postmenopausal period, bone loss results from an imbalance in bone resorption, relative to formation. The major cause of the loss of bone after menopause is estrogen deficiency, although other factors play a role, particularly with advancing age. During the first few years after menopause, estrogen deficiency is presumably the predominant factor in producing the accelerated rate of bone loss.

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[1] Several tables and figures have been reproduced from the electronic submission. Owing to technical problems with the electronic submission, some of the sponsor's data tables have been modified to accommodate format. Reviewer's tables are indicated as such. All figures are those of the sponsor.

[2] Reviewer's **comments** appear in **bold print** throughout this review and are indicated accordingly.

Strategies for the prevention of postmenopausal osteoporosis include adequate daily intake of calcium and vitamin D, maintenance of reasonable body weight and level of exercise, cessation of smoking, and avoidance of excessive intake of caffeine. In principle, pharmacological intervention can be directed at decreasing bone resorption (anti-resorptive agents), or increasing bone formation (anabolic agents). Approved classes of anti-resorptive agents include hormone (estrogen) replacement therapy, calcitonin, selective estrogen receptor modulators, and bisphosphonates. Each class of drug has advantages and disadvantages. At the time of this review, there are no FDA-approved effective anabolic agents for bone.

Hormone replacement therapy (HRT) with estrogen is well established as an effective modality for the prevention of bone loss after menopause. Approved routes of administration of HRT include oral and transdermal. Transdermal administration of 17β-estradiol has been widely used for HRT, with benefits that are generally comparable to those that accompany orally administered estrogens. Transdermal estradiol does not undergo first pass hepatic metabolism and consequently, very little estradiol is metabolized to estrone. The clinical significance of this difference is not clear, although estradiol is more potent than estrone. Estradiol has a short half-life in plasma; therefore, levels of the hormone decline rapidly following removal of the transdermal delivery system.

A transdermal estradiol system (Estraderm®, with nominal delivery rate of 0.05 mg and 0.1 mg/day) is currently approved for the treatment of postmenopausal vasomotor symptoms and prevention of postmenopausal osteoporosis. The subject of the present review, Vivelle®, contains 17-β estradiol in an adhesive platform with a thinner patch. According to the sponsor, the Vivelle patch provides "possibly greater wearing comfort and a more uniform plasma E2 level than Estraderm, a reservoir type transdermal system."

Vivelle (in doses of 0.0375 mg, 0.05mg, 0.075 mg and 0.1 mg) has been approved for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. Included in the (approved) indications are moderate to severe postmenopausal vasomotor symptoms and vulval and vaginal atrophy. The present trial was designed to evaluate the efficacy of four doses of Vivelle (0.025 mg, 0.0375 mg, 0.05 mg, and 0.1 mg) in the prevention of postmenopausal bone loss.

The sponsor has also conducted three phase 4 studies (currently under review by DRUDP): a placebo-controlled, 12-week study of multiple doses of Vivelle in the treatment of menopausal symptoms, and two 3-week placebo- and active (Climara®)-controlled skin irritation studies. These are included in the Integrated Summary of Safety, in this review. In addition, the sponsor has submitted reprints of published data on efficacy of Menorest® (a transdermal estradiol system that is identical to Vivelle and that is marketed outside the US and Canada by Rhone-Poulenc Rorer).

7 DESCRIPTION OF CLINICAL DATA SOURCES

Clinical data (safety and efficacy) were obtained from the women who participated in the submitted trial (sponsor's Trial 035). In addition, data from the most recent 120-day safety update were reviewed, together with an Integrated Safety Summary. Individual case report forms were also reviewed. Finally, the published safety and efficacy data on Menorest were also reviewed.

8 CLINICAL STUDIES

8.1 Reviewer's trial #1, Sponsor's Protocol # 035

"A randomized, modified double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and the dose-response of a new estradiol matrix transdermal therapeutic system in the prevention of postmenopausal bone loss"

8.1.1.1 Objectives

This was the pivotal clinical study that was designed to support the osteoporosis prevention claim for Vivelle. The study had three primary and three secondary objectives. As stated by the Sponsor, these were:

Primary Objectives

- *To demonstrate the efficacy and the dose-response of Vivelle with respect to the prevention of postmenopausal bone loss of the lumbar spine*
- *To determine the minimum effective dose of Vivelle for the prevention of postmenopausal bone loss of the lumbar spine*
- *To assess the systemic and local safety and tolerability of chronic (2 year) treatment with Vivelle in postmenopausal women*

Secondary Objectives

- *To demonstrate the efficacy and dose-response of Vivelle with respect to the prevention of postmenopausal bone loss of the femoral neck and whole body*
- *To assess the effects of Vivelle, compared to that of placebo, on urinary excretion of cross-linked N-telopeptides of type I collagen (NTx), and serum osteocalcin, markers of bone resorption and formation, respectively*
- *To assess the correlation between the changes in the bone mineral density (BMD) and changes in the urinary/serum concentrations of the above*

markers of bone turnover in postmenopausal patients treated with Vivelle and placebo

8.1.1.2 Study design

Study 035 was a two-year multicenter (20 centers), randomized, placebo-controlled, parallel group trial in postmenopausal women. The trial employed a modified double-blind design (double-blind with respect to treatment, active vs placebo, but not to treatment dose). Subjects were stratified according to whether they had a prior hysterectomy.

Comments: The trial enrolled only recently (≤ 5 years) postmenopausal women. This is the period of accelerated bone loss following estrogen withdrawal and the period in which estrogen replacement is most effective. It is also the time during which the smallest estrogen doses would be expected to show maximum efficacy. As with any estrogen preparation, the bone efficacy can be expected to decline somewhat if tne drug is introduced after the period of accelerated bone loss. Comments regarding stratification according to hysterectomy status, as well as potential effects of concomitant progestational agents appear below.

The trial had 5 treatment arms, with random patient allocation in a 1:1:1:1:1 distribution:

Vivelle 0.025 mg/day (7.25 cm^2)

Vivelle 0.0375 mg/day (11 cm^2)

Vivelle 0.05 mg/day (14.5 cm^2)

Vivelle 0.10 mg/day (29 cm^2)

Placebo (7.25 cm^2 or 11 cm^2 or 14.5 cm^2 or 29 cm^2)

The trial period was 2 years. The treatment systems were applied twice weekly, and post-treatment evaluations were performed after 13, 26, 52, 78 and 104 weeks.

A schematic diagram of the trial design is provided below:

PERIOD	SCREENING	RANDOMIZATION	POST-TREATMENT EVALUATIONS
Visit	1	2	3 4 5 6 7
Week	-3 to –1	1*	13 26 52 78 104
Double-Blind Treatment†		Vivelle 0.025 mg/day (7.25 cm^2) OR Vivelle 0.0375 mg/day (11 cm^2) OR Vivelle 0.05 mg/day (14.5 cm^2) OR Vivelle 0.1 mg/day (29 cm^2) OR Placebo (7.25/11/14.5/29 cm^2)**	
* Day 1, baseline ** Only one patch size per patient † Blinded to treatment (i.e., active versus placebo), not to dose			

Comments: This design should minimize, but not entirely eliminate, investigator and patient bias in assessment of safety and efficacy outcomes. Possible dose-related estrogen effects on genito-urinary system symptoms, hot flashes, and other subjective menopause-associated phenomena may be a source of "unblinding." This, of course, is unavoidable. Since the major efficacy outcomes are radiographic and biochemical, this potential unblinding should have minimal impact on the study. However, these considerations relate more closely to conclusions regarding the local and systemic safety/tolerability profile of various doses of Vivelle.

The sponsor did not employ a double-dummy technique for blinding with respect to dose because preparation of multiple doses with a single patch size was impractical.

Patients with an intact uterus received concomitant medroxyprogesterone acetate (MPA), and the sponsor stratified subjects based on hysterectomy status to ensure a balance between those receiving MPA and those not taking a progestational agent.

Comments: Such stratification is reasonable, because of (largely theoretical) concerns that a progestational agent may interfere with

estrogen action on bone. It should be noted that there are by now available data demonstrating that this is not a significant concern with MPA added to estrogen replacement therapy.

Further comments:

1) The two-year trial duration should provide sufficient time to detect the anticipated changes in all the efficacy variables. There is by now vast clinical experience with numerous estrogen preparations. Therefore, the exposure afforded by this trial should be sufficient to provide adequate safety and tolerability data on Vivelle, given the extensive safety data base on estrogen use in the postmenopausal period, together with additional data on Vivelle and Menorest (supplied by the sponsor and reviewed below in the analysis of safety).

2) The higher Vivelle dose selections (0.05 mg/day and 0.1 mg/day) were based on the known efficacy and safety of Estraderm®, while the two lower doses (0.025 mg/day and 0.0375 mg/day) were included to establish the minimum effective dose of the transdermal system. This is clinically important, because the current trend in practice is attempt to limit the estrogen dose for HRT.

3) With respect to age selection for the trial population, see above comment regarding enhanced efficacy of estrogens in the period immediately following estrogen withdrawal.

8.1.1.3 Protocol

8.1.1.3.1 Population

The trial population consisted of healthy postmenopausal women, age ≥ 45 years, not more than 5 years past natural menopause. Subjects were to have lumbar spine BMD t-scores ≥ -2 (i.e., non-osteoporotic).

Thirty-six "completed" patients were to be randomized into each of the 5 treatment groups. The sponsor defines a "completed" patient as one who met all the inclusion/exclusion criteria and completed the two-year trial. Included in this population were patients who discontinued due to significant bone loss or endometrial hyperplasia. The sponsor sought to enroll approximately 224 patients into the trial, in order to allow for patient dropouts.

Comments: For clarification, patients who dropped out for reasons other than lack of bone efficacy or endometrial hyperplasia are not classified as completers. For analysis, the sponsor has defined five population subsets: randomized, completed, intent-to-treat, acceptable for efficacy, and safety. Formal definitions of these analytical groupings appear below. A summary

of the number of patients in each group appears in the Results section below.

The sponsor has provided the following list of inclusion/exclusion criteria for entry into the trial:

INCLUSION CRITERIA

- Hysterectomized or nonhysterectomized postmenopausal female outpatients 45 years of age or older except as follows: patients hysterectomized before the onset of menopause had to be between the ages of 51 and 56; there was no age requirement for surgically menopausal patients
- Patients must be either surgically menopausal (bilateral oophorectomy) at least 6 weeks prior to entering the trial (surgery date was considered the onset of menopause), or naturally menopausal (cessation of menses for at least 12 months), for no longer than 5 years
- Serum estradiol (E2) levels of ≤ 24 pg/ml and follicle stimulating hormone (FSH) levels of ≥ 40 mIU/ml
- Bone mineral density (BMD) of L1-L4 AP, no more than 2 standard deviations below the mean peak BMD for premenopausal women (i.e., ≥ 0.827g/cm^2) as assessed by dual energy x-ray absorptiometry (DEXA)

EXCLUSION CRITERIA

- Carcinoma of breast at any time or any other malignancy within the past 5 years (except carcinoma of cervix in situ and fully treated localized basal cell carcinoma of the skin), endometrial hyperplasia, endometriosis, thrombophlebitis, thromboembolic disorders, generalized active skin disorder likely to affect patch tolerability, blood disorders, cardiovascular disease, renal disease, gastrointestinal disease, pituitary disease, metabolic bone disease, systemic granulomatous disease, uncontrolled thyroid disease or diabetes mellitus, parathyroid disease, liver and/or gallbladder disease
- Allergy to topical products containing any of the ingredients of the test systems
- Hypersensitivity to MPA if patient had an intact uterus
- Known or suspected alcoholism or drug abuse within 5 years
- Undiagnosed vaginal bleeding within past 6 months
- Patients experiencing hot flushes and/or other menopausal symptoms sufficiently severe as to exclude placebo treatment
- Nontraumatic vertebral fracture
- Uncontrolled hypertension
- Evidence of overt Vitamin D deficiency
- Any clinically significant condition that might in the opinion of the investigator compromise patient's safety, interfere with the trial evaluations, or preclude completion of the trial
- Any investigational drug within 30 days, previous estrogen or progesterone treatment of any form within 6 months for women treated with HRT for 3 months or longer, and 8 weeks for

women treated with HRT for less then 3 months, high doses of vitamin D or calcitonin within 2 months, androgens or anabolic steroids within 6 months, bisphosphonates or pharmacological doses of fluoride exceeding 1 month, systemic corticosteroids in the past 6 months, concomitant treatment with any medication that may affect bone calcium metabolism or interfere with bone metabolism

- Patients with laboratory test results obtained at Visit 1 deviating from those listed in the protocol

Comments: These are reasonable, safe, and generally standard criteria for a study of estrogen in the prevention of postmenopausal osteoporosis. It is noteworthy that the sponsor provides no information regarding methodology for patient recruitment, the number of patients initially contacted, the number of patients who were screened, the number that failed to meet inclusion/exclusion criteria, and the reasons for such failure. These considerations are important in making a judgment regarding the degree to which any trial population represents the intended marketing population. Unfortunately, such information is frequently lacking from new drug applications and efficacy supplements. "Evidence of overt vitamin D deficiency" is not defined in the text.

8.1.1.3.2 Procedures

Procedures for randomization and blinding are described in detail in the NDA submission. The sponsor anticipated that there would be more dropouts from the placebo groups; therefore, the treatment assignment ratio was maintained at 3:1 (active:placebo), despite the fact that there were 4 active treatment doses.

Following screening and randomization, patients were placed on one of the following transdermal delivery systems, designed to deliver a given dose of estradiol or placebo:

Vivelle (estradiol matrix transdermal therapeutic system)

Dose Forms	Strengths (Nominal delivery)	Application Frequency
7.25 cm^2 patch	0.025 mg/day	Twice a week
11 cm^2 patch	0.0375 mg/day	Twice a week
14.5 cm^2 - patch	0.05 mg/day	Twice a week
29 cm^2 patch	0.1 mg/day	Twice a week

Placebo (matching matrix transdermal therapeutic systems)

Dose Forms	Strengths (Nominal delivery)	Application Frequency
7.25 cm^2 patch	0	Twice a week
11 cm^2 patch	0	Twice a week
14.5 cm^2 patch	0	Twice a week
29 cm^2 patch	0	Twice a week

As detailed above, the placebo group received test systems that were identical in size and shape to one of the active treatments. The patients were thus blinded with respect to treatment (active versus placebo) and not to the dose levels of drug.

Patients applied the test system twice weekly to a skin area (buttock or abdomen) that was clean, dry, and unbroken. The sponsor permitted contact of the test system with water: patients were permitted to bathe, shower, or swim. In the event that a patch fell off, it was reapplied. If necessary, the displaced patch was replaced with a new one. Details relating to storing and dispensing the test systems are provided in the NDA application.

The clinical investigators, Novartis personnel, and others involved in the monitoring or conducting of the trial were blinded to the post-treatment BMD and bone marker results, as well as trial drug codes.

A central laboratory analyzed the BMD scans. This facility was responsible for identifying patients with excessive bone loss (≥ 6% at the 26- or 52-week

evaluation, or ≥ 8% at the 78-week evaluation). These results were immediately sent to the investigator, who was responsible for the decision to continue the patient in the trial.

Concomitant medications: All patients received calcium carbonate 500 mg (1 tablet of Os-cal 500) b.i.d., with meals, throughout the trial. All of the patients who had not undergone hysterectomy also received medroxyprogesterone acetate (MPA), 2.5 mg p.o. per day throughout the trial.

Comments: Postmenopausal women generally require 1500 mg of elemental calcium per day to maintain mineral balance. The 1000 mg supplement is probably adequate, if patients' diets contain appreciable calcium. Patients in this age group should generally be supplemented with vitamin D, 400-800 IU daily. Thus, these patients were not optimally supplemented during the trial. It should be noted that "evidence of overt vitamin D deficiency" constitutes an exclusion criterion (see above) for entry into the trial. However, the clinical data section has no description of the methodology employed for making this determination. Establishment of vitamin D status and adequate replacement regimens are an important feature of osteoporosis trials. Failure to account for vitamin D status and ensure that women are adequately supplemented is substandard medical practice and is a deficiency in the research protocol.

The MPA regimen (2.5 mg p.o. daily) for women with an intact uterus is generally accepted practice.

For the duration of the trial, patients were not permitted to take any medication listed under the exclusion criteria. If any other medication was deemed medically necessary, that medication was permitted after consulting with the trial physician. Exceptions to this were OTC medications such as analgesics, cough/cold preparations or antihistamines. These were permitted without prior consultation with the trial physician. All concomitant medications taken during the trial were recorded on the CRF.

Treatment compliance: The sponsor recorded (on the CRF) the number of test systems dispensed and the number of unused systems returned at each visit.

The sponsor also recorded study medication used, dosages administered, and intervals between visits.

Schedule of procedures: The sponsor has provided the following tabular summary of the trial procedures and schedule. Details regarding specific safety and efficacy determinations are provided in the appropriate sections below.

Phase	Screen	Double-Blind Treatment					
Visit	1	2	3	4	5	6	7
Trial Period	Wk -1 to -3	Day 1	Wk 13	Wk 26	Wk 52	Wk 78	Wk 104
Informed Consent	X						
Medical History	X						
Complete Phys./Gyn. Exam	X						X
Interim Exam		X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X
Electrocardiogram	X						
X-ray – Thoracic Lumbar Spine	X						
Lab Safety Tests	X				X		X
Lab Screening Tests	X						
Papanicolaou Smear	X				X		X
Mammography	X				X		X
Endometrial Biopsy (if uterus intact)	X						X
BMD: Lumbar Spine, Femoral Neck	X			X	X	X	X
BMC: Total Body	X				X		X
Bone Markers	X		X	X	X	X	X
Randomization		X					
Dispense Medications		X	X	X	X	X	
Vaginal Bleeding Assessment (if uterus intact)			X	X	X	X	X
Adverse Experiences		X	X	X	X	X	X
General Instructions on Physical Exercise	X	X	X	X	X	X	X
Termination Sheet							X

Laboratory determinations employed standard methodology and were performed at a central facility (details in NDA). DEXA scans were performed by ——— certified DEXA operators, who received protocol-specific training. Raw DEXA scan data were copied on an ——————— . The —, the patient scan log, instrument maintenance report, and instrument QC data archive were sent to ——— MDM. DEXA scans were analyzed at ——— MDM. All scan data were entered in the ——— MDM patient file.

Details of DEXA quality control methodology are provided in the NDA. Cross-calibration studies were performed to assess intra- and inter-instrument variability. These used ——————————— that contained known quantities of bone-like material.

——— MDM was responsible for identifying any subject with excessive bone loss during the trial (≥ 6% at the 26- or 52-week evaluation or ≥ 8% at the 78-week evaluation). The BMD results for these patients were faxed to the investigator, who then informed ——— MDM whether the patient was to be continued in the trial.

Details regarding management and quality control of data are provided in the NDA application.

All clinical laboratory samples were performed in a central laboratory ——— ———.

Discontinuation from treatment:

The sponsor provides the following list of events that were sufficient for discontinuation from the trial:

- Whenever the patient decided that it was in her best interest
- Whenever the investigator considered it advisable or in the patient's best interest
- Intolerable adverse experiences; patients found to have endometrial hyperplasia/cancer at any time during the trial were to be discontinued from the trial and treated appropriately
- Lack of therapeutic response as defined by L1-L4 AP DEXA scan demonstrating bone loss of ≥ 6% at the 26 week (6 month) or 52 week (12 month) time point, or ≥ 8% at the 78 week (18 month) evaluation time point and considered advisable by the investigator
- Major violation of the clinical trial protocol after discussion with the Medical Trial Specialist
- Non-compliance of the patient
- Development of any exclusion criteria
- Lost to follow up
- Administrative problem e.g., transfer out of town

If a patient discontinued prematurely and had received at least one dose of trial medication, the following assessments were to be done: a full physical, including gynecological, examination; Pap smear and other laboratory safety tests; endometrial biopsy (nonhysterectomized patients); mammography; recording of concomitant medications; assessment of AE's; BMD determinations; and measurement of bone markers (if not performed within 3 months prior to discontinuation).

Comments: This methodology is appropriate for a study of safety outcomes, as discussed further in Comments, section 8.1.1.4.2 below.

Subjects who terminated from the trial prematurely were not replaced.

The efficacy analysis excluded subjects who did not have a baseline measurement and at least one valid post treatment measurement.

8.1.1.3.3 Concurrent therapy

See above for description and discussion of calcium, MPA, and OTC drugs that were concurrently administered.

8.1.1.4 Endpoints

8.1.1.4.1 Efficacy

The primary efficacy variable was the percent change from baseline in BMD of the AP lumbar spine (L1-L4), measured by DEXA at Week 104.

The sponsor has specified a number of secondary efficacy endpoints:

- Percent change from baseline in BMD of the L1-L4, AP at Visits 4, 5, 6 (Weeks 26, 52, 78)
- Percent change from baseline in BMD of the lateral lumbar spine (L2-L4, lateral) at Visits 4, 5, 6, 7 (Weeks 26, 52, 78, 104)
- Percent change from baseline in BMD of the femoral neck at Visits 4, 5, 6, 7 (Weeks 26, 52, 78, 104)
- Percent change from baseline of the total body mineral content (BMC) at Visits 5, 7 (Weeks 52, 104)
- Percent change from baseline in serum osteocalcin at Visits 3, 4, 5, 6, 7, (Weeks 13, 26, 52, 78, 104)
- Percent change from baseline in urinary NTx creatinine ratio at Visits 3, 4, 5, 6, 7 (Weeks 13, 26, 52, 78, 104)

8.1.1.4.2 Safety analyses and endpoints

Safety population: All patients who received at least one dose of test treatment were included in the safety analysis.

Safety assessments: Assessment of safety and tolerability of Vivelle were based on incidence and severity of clinical and laboratory AEs, compared to placebo.

The clinical safety variables were: all clinical AEs, and changes in vital signs, weight, and height, compared to baseline.

Laboratory safety monitoring included: routine lab tests (changes in CBC, serum chemistry and urinalysis), Pap test, endometrial histology (biopsy), and mammography. Full technical descriptions of the analytic methodology for safety

analyses are included in the application. The schedule for routing monitoring appears as part of the table above.

The sponsor provides the following criteria for clinically notable laboratory and vital sign abnormalities (significant changes from baseline):

- *hemoglobin, hematocrit: -10%*
- *leukocytes, neutrophils, lymphocytes count: -30%, +30%*
- *platelet count: -25%*
- *serum SGOT/AST, SGPT/ALT, total bilirubin, creatinine: +50%*
- *serum alkaline phosphatase: +25%*
- *serum total cholesterol, triglycerides: -20%, +20%*
- *serum HDL, LDL cholesterol: -5%, +5%*

Systolic blood pressure (mmHg): less than 90 and a decrease of at least 20 from screening; greater than 180 and an increase of at least 20 from screening

Diastolic blood pressure (mmHg): less than 50 and a decrease of at least 15 from screening; greater than 105 and an increase of at least 15 from screening

Pulse (bpm): less than 50 and a decrease of at least 15 from screening; greater than 120 and an increase of at least 15 from screening

Weight (kg): increase or decrease of at least 7% from screening

Comments: The plan for safety monitoring is appropriate for a study of estrogen in this population, given that non-hysterectomized patients will take a progestational agent. The schedule for mammograms, endometrial biopsy assessments, and Pap smears is within acceptable practice guidelines for a clinical trial of this nature. The planned clinical and laboratory evaluation of patients who terminated prematurely was appropriate. The evaluation would minimize loss to follow-up and ensure adequacy of the safety data.

8.1.1.4.3 Statistical methods and considerations

A complete statistics review accompanies the medical review. The following is a brief description of clinically relevant statistical and trial design issues.

Comparability of treatment groups: The sponsor evaluated treatment group comparability on the basis of demographic and baseline characteristics (see below for specific characteristics). The resulting p-values have been provided for descriptive purposes.

Efficacy outcome variables: The primary and secondary efficacy variables are listed above (in section **8.1.1.4.1**).

Discontinuations: For patients who discontinued the trial for unsatisfactory therapeutic effect (lumbar spine bone loss of ≥6% at the 26-week or 52-week time point or ≥8% at 78 weeks) or for endometrial hyperplasia, the last measurements were to be carried forward to the subsequent time points (in fact, this applied to two patients in the trial). If a specific endpoint was not available for any other reason, data were not carried forward. In addition, the patient was not included in the analysis at that time point.

As requested by FDA at a pre-NDA meeting, the sponsor conducted an exploratory analysis of the primary efficacy variable. The last observation for all randomized patients (whether or not they satisfied the above criteria) was carried forward in this analysis. If a patient did not have a post-baseline measurement, her baseline measurement was carried forward.

Populations for analysis:

The sponsor defined the following populations for data analysis:

1) Randomized population: all patients who were randomized into the trial.

2) Safety population: all patients who received at least one test treatment dose and had at least one post-baseline safety evaluation. This population was used for analysis of all safety data, as well as for all summary and listing data pertaining to safety.

3) Treated population: all patients who received at least one dose of a test treatment.

4) Intent-to-treat (ITT) population: all randomized patients who had a valid baseline and post-baseline efficacy measurement.

5) Acceptable for efficacy (ACC) population: all patients who met the inclusion/exclusion criteria and who had a valid baseline and post-baseline measurement. Note that the decision regarding satisfaction of inclusion/exclusion criteria was agreed upon, prior to unblinding of the trial, by the clinical trial monitor and the trial statistician.

In the clinical data section, the sponsor states that the ITT population was used for analysis of the primary and secondary efficacy variables. As pre-specified in the analysis plan, if more than 10 patients were determined not to be "acceptable for efficacy", a secondary analysis was to be conducted using the ACC population. In fact, there were only five patients who were not acceptable for efficacy, and the secondary analysis was not conducted.

Comments: As discussed further below, the efficacy results that are presented in the clinical data section are in fact based on a completers analysis, rather than a true ITT analysis. Accordingly, conclusions regarding efficacy, and the labeling claims made consequent to these conclusions, should be understood as based on a completers analysis.

Analysis of population characteristics:

The following baseline variables were compared across treatment groups. For this analysis, the sponsor used a one-way analysis of variance F-test for continuous variables and the Chi-square test of homogeneity for categorical variables:

- Age (continuous)
- Race
- Baseline AP L1-L4 lumbar spine BMD
- Baseline serum osteocalcin
- Baseline urinary NTx creatinine ratio
- Whether or not the patient had a hysterectomy
- Type of menopause (surgical or natural)
- Months since menopause
- Smoking history

Efficacy evaluations:

BMD outcome variables were summarized separately at Weeks 26, 52, 78, and 104. Total body BMC was summarized Weeks 52 and 104.

Serum osteocalcin and urinary NTx/creatinine ratios were summarized at Weeks 13, 26, 52, 78, and 104.

Analytical methods: The sponsor used an ANOVA model (with treatment, menopause type [natural vs surgical], and treatment by menopause interaction) to compare the treatment groups with respect to % change from baseline in BMD variables, total body BMC, and bone formation and resorption markers. To compare effects of the Vivelle doses with placebo, the sponsor used Dunnett's multiple comparison procedure at an overall 0.05 level of significance (two-sided). Comparisons between the Vivelle doses used a t-test with the pooled mean square error term from the ANOVA at the 0.05 level of significance (two-sided). In addition, summary statistics are provided by center. However, center was not included in the model as all of the efficacy data were analyzed by one central laboratory and center-by-treatment cell size was anticipated to be small.

In addition, the sponsor provides summary statistics of the primary efficacy variable by age group (<45 years and ≥ 45 years) and by menopause type (natural or surgical).

The sponsor performed a dose-response analysis of % percent change from baseline in lumbar spine BMD at each visit. A paired t-test was used to analyze within-treatment-group BMD changes from baseline to Week 104.

The exploratory analysis used simple linear regression to assess the correlation between the change from baseline in bone markers (serum osteocalcin and NTx /creatinine ratios at Weeks 13, 26, 52, 78, and 104), and reduction in lumbar spine BMD from baseline to Week 104.

Safety evaluations:

Safety population: The sponsor summarized safety variables for the entire safety population (all those receiving at least one dose of the test treatment and having at least one post-baseline safety evaluation), by treatment group. Vaginal bleeding assessments and endometrial biopsy results are included only for patients with an intact uterus.

Summary of AEs: AEs reported over the entire trial were summarized by treatment group, drug-relationship and severity. Deaths, serious AEs, and other significant AEs were summarized by patient.

Means and changes from baseline in blood pressure, pulse and weight were summarized by treatment group and visit. Frequency of patients with clinically notable vital signs were summarized by treatment group and visit.

Clinical laboratory abnormalities are presented by patient and by individual tests. For hematology and serum chemistry safety tests, means, medians and changes from baseline in the means and medians are given by treatment group and visit.

Power analysis and sample size considerations:

The sponsor based the sample size calculation on data taken from a selected group of Estraderm-treated patients. The goal of 36 completed patients per treatment arm was calculated based on % change in lumbar spine BMD for this group (variance = 33%). The assumptions were an overall significance of 0.05 (two-sided, using Dunnett's multiple comparison procedure), a power of 80%, a minimum difference from baseline of 4% in lumbar spine BMD between placebo and the 0.10 mg/day (highest) dose after two years of therapy, and a minimum change from baseline of 3.5% between placebo and the second highest dose (0.05 mg/day).

Interim analyses: No interim analysis was planned or carried out.

Other: The sponsor summarized changes from baseline in height at Week 104 and terminal visit for all safety patients.

8.1.2 Results

8.1.2.1 Populations enrolled/analyzed

Two hundred sixty-one patients were randomized into the trial; all of these were treated with the test drug, since each patient received the trial medication on the randomization day.

As shown in the table below, with the exception of 2 patients who were lost to follow-up and had no safety evaluations, the safety population equals the total randomized population.

The ITT population consisted of 239 patients. As shown in the table below (abstracted from the sponsor's table 7.1-1, reproduced below), these were most of the total randomized into each treatment arm (range 86% to 100%).

PATIENT DISPOSITION

	Vivelle 0.1 mg/day	Vivelle 0.05 mg/day	Vivelle 0.0375 mg/day	Vivelle 0.025 mg/day	Placebo
Randomized	49	53	45	47	67
Completed	30	39	34	37	46
Intent-to-treat population	42	48	41	47	61
Safety population	49	53	43	47	67

Not shown in the table, but included in the sponsor's data, 234 of these 239 were deemed acceptable for efficacy evaluation. The remaining 5 patients who were excluded from the ITT analysis had protocol violations due to administration of glucocorticoids. Three were in the 0.05 mg/day group, with one each in the placebo and 0.025 mg/day group (data in table 7.2-1 and text of NDA submission).

Completers: A total of 186 patients (71.3%) completed the trial and 75 (28.7%) patients discontinued from the trial prematurely. From the data in the table, the % dropouts ranged from 39% in the highest dose group to 21% in the 0.025 mg group. Thirty-one % of patients in the placebo group failed to complete the trial.

Protocol violations: Protocol deviations occurred in 29% of patients. These were equally distributed across all 5 treatment arms. A review of these discloses that they were minor and not likely to affect outcomes.

Twenty-seven patients discontinued the trial prematurely due to AEs; 12 of these were in the highest dose group. Discontinuation due to AEs occurred more frequently in active treatment groups than placebo. Further details regarding each prematurely discontinued patient are given below. Only two patients discontinued from the trial due to an unsatisfactory therapeutic effect; both belonged to the placebo group. The sponsor's table 7.1-2 summarizes the frequency distribution of patients prematurely discontinued from the trial by visit for each treatment group. A summary of patient disposition by treatment group is provided in the table below:

Table 7.1-1
Patient disposition by treatment group
(All randomized patients)

	Vivelle 0.1 mg/day (N=49) N (%)	Vivelle 0.05 mg/day (N=53) N (%)	Vivelle 0.0375 mg/day (N=45) N (%)	Vivelle 0.025 mg/day (N=47) N (%)	Placebo (N=67) N (%)
No. randomized	49 (100.0)	53 (100.0)	45 (100.0)	47 (100.0)	67 (100.0)
No. completed	30 (61.2)	39 (73.6)	34 (75.6)	37 (78.7)	46 (68.7)
No. treated	49 (100.0)	53 (100.0)	45 (100.0)	47 (100.0)	67 (100.0)
No. discontinued	19 (38.8)	14 (26.4)	11 (24.4)	10 (21.3)	21 (31.3)
Reasons for discontinuations					
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse experience(s)	12 (24.5)	5 (9.4)	4 (8.9)	4 (8.5)	2 (3.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)
Does not meet protocol criteria	1 (2.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (3.0)
Other	6 (12.2)	8 (15.1)	7 (15.6)	6 (12.8)	15 (22.4)
In primary efficacy analysis					
All intent-to-treat patients	42 (85.7)	48 (90.6)	41 (91.1)	47 (100.0)	61 (91.0)
All acceptable for efficacy patients	42 (85.7)	45 (84.9)	41 (91.1)	46 (97.9)	60 (89.6)
In safety analysis					
Adverse event evaluation	49 (100.0)	53 (100.0)	43 (95.6)	47 (100.0)	67 (100.0)
Safety laboratory evaluation	49 (100.0)	53 (100.0)	43 (95.6)	47 (100.0)	67 (100.0)

Source: Post-text table 7.1-1

Comments: The overall retention of patients throughout the course of the trial is acceptable. The largest number of dropouts occurred in the highest dose group (0.10 mg), and these were due mainly to adverse events. These AEs are analyzed and discussed below. Aside from this subgroup, there was no gross imbalance of dropouts from specific efficacy or safety populations, by treatment arm. However, it is important also to consider dropouts within each treatment arm as a function of time throughout the entire trial. These data are provided by the sponsor in the following table:

Post-text table 7.1-2
Frequency distribution of patients who prematurely discontinued from the trial by treatment group and visit
(All randomized patients)

	Vivelle 0.1 mg/day (N=49) N(%)	Vivelle 0.05 mg/day (N=53) N(%)	Vivelle 0.0375 mg/day (N=45) N(%)	Vivelle 0.025 mg/day (N=47) N(%)	Placebo (N=67) N(%)	Total (N=261) N(%)
Cumulative number of patients who prematurely discontinued prior to						
Day 1 (Visit 2)	0 (0.0)	0 (0.0)	2 (4.4)	0 (0.0)	0 (0.0)	2 (0.8)
Week 13 (Visit 3)	9 (18.4)	5 (9.4)	2 (4.4)	1 (2.1)	6 (9.0)	23 (8.8)
Week 26 (Visit 4)	14 (28.6)	6 (11.3)	6 (13.3)	4 (8.5)	12 (17.9)	42 (16.1)
Week 52 (Visit 5)	15 (30.6)	12 (22.6)	11 (24.4)	8 (17.0)	16 (23.9)	62 (23.8)
Week 78 (Visit 6)	17 (34.7)	13 (24.5)	11 (24.4)	10 (21.3)	20 (29.9)	71 (27.2)
Week 104 (Visit 7)	19 (38.8)	14 (26.4)	11 (24.4)	10 (21.3)	21 (31.3)	75 (28.7)
Mutually exclusive number of patients who prematurely discontinued prior to						
Day 1 (Visit 2)	0 (0.0)	0 (0.0)	2 (4.4)	0 (0.0)	0 (0.0)	2 (0.8)
Week 13 (Visit 3)	9 (18.4)	5 (9.4)	0 (0.0)	1 (2.1)	6 (9.0)	21 (8.0)
Week 26 (Visit 4)	5 (10.2)	1 (1.9)	4 (8.9)	3 (6.4)	6 (9.0)	19 (7.3)
Week 52 (Visit 5)	1 (2.0)	6 (11.3)	5 (11.1)	4 (8.5)	4 (6.0)	20 (7.7)
Week 78 (Visit 6)	2 (4.1)	1 (1.9)	0 (0.0)	2 (4.3)	4 (6.0)	9 (3.4)
Week 104 (Visit 7)	2 (4.1)	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.5)	4 (1.5)
Total number discontinued	19 (38.8)	14 (26.4)	11 (24.4)	10 (21.3)	21 (31.3)	75 (28.7)

Source: DISK$VIVE035:[VIVE035.STAT.PGM.ANALYSIS.TABLES]T07_1_2.SAS 26APR1999@12:27

Aside from the few extra early dropouts at Weeks 13 and 26 in the 0.10 mg group, there is no obvious imbalance, across treatment arms, in the frequency distributions over time. In fact the placebo group lost 12 patients by Week 26, compared to 14 patients in the highest dose (0.10 mg) group at the same time point.

Overall, the patient retention rates for this trial are adequate to ensure reliable efficacy and safety data.

However, as discussed below, the major efficacy analyses were not based on the ITT population. Instead, these are based on a population of patients who completed the 104 weeks (see below). These considerations are at

variance with the sponsor's headings in most of the figures and tables that are presented in the clinical data section and in the proposed labeling.

Population demographics: With respect to baseline characteristics (race, age, hysterectomy status, type of menopause, time since menopause, smoking status, L1-L4 BMD, serum osteocalcin, urinary NTx creatinine ratio), there were no statistically significant differences across treatment groups for both the ITT and all randomized patient populations.

Baseline demographics and background characteristics are summarized by treatment group for all ITT and safety patients, in Post-text tables 7.4-2A and 7.4-2B. In addition, the sponsor has provided a list of the statistical tests used to determine baseline comparability across the treatment groups (Tables 7.4-1a and 1b). There were no statistically significant differences in any of these parameters across treatment groups. These tables will not be reproduced here. Instead, to indicate the nature of the entire trial population, each parameter is given for the total ITT population (N= 239) in the (reviewer's) table below:

Mean age (yr)	weight kg	height cm	BMI Kg/m2	race	smoker	Meno-pause type	Months since meno-pause	Prior HRT	Hyster-ectomy
52.00 (27.4-61.9)	72.9 (49-70)	160.8 (132.5-185)	28.2 (19.1-45.1)	92.1% white	17.2% yes	81.6% natural	31.65 (1.6-71.7)	6.7% yes	61.1% yes

The characteristics of the safety population (N=259) are all essentially the same as those of the ITT population and will not be reproduced here.

Comments: Most women entering osteoporosis trials are white, and a significant number are smokers. This trial population is somewhat younger than the typical osteoporosis study group, because of the intended proximity to menopause. The average BMI is somewhat higher than that which is usually encountered in osteoporosis trial populations, or in the osteoporotic population in general. Postmenopausal women with higher BMI's have increased levels of circulating estrogens, principally estrone (which is formed by peripheral aromatization of androstenedione). It is of interest to examine the effects of low level estrogen replacement in the heavier strata of patients.

8.1.3 Efficacy endpoint outcomes

8.1.3.1 Primary efficacy endpoint

The primary efficacy endpoint variable was the % change from baseline in BMD of the L1-L4 AP lumbar spine at Week 104. As shown in the following table (sponsor's table 9.1-1), the placebo patients lost an average BMD of about 2% from baseline, whereas all 4 of the treated groups gained spinal BMD. The largest BMD gains were in the higher dose groups. The table presents data for all 5 treatment arms and according to MPA treatment status:

Table 9.1-1
Bone mineral density (g/cm**2) - L1-L4 AP lumbar spine
Percent change from baseline at week 104 by MPA status
(All intent-to-treat patients)

Treatment with MPA	Statistic	Vivelle 0.1 mg/day (N=42)	Vivelle 0.05 mg/day (N=48)	Vivelle 0.0375 mg/day (N=41)	Vivelle 0.025 mg/day (N=47)	Placebo (N=61)
Yes	N	6	12	13	19	19
	MEAN	6.812	5.522	2.919	1.486	-2.264
	SD	2.132	4.195	1.794	4.360	4.191
No	N	23	25	19	18	26
	MEAN	5.692	2.201	1.365	2.143	-1.771
	SD	3.694	3.579	4.124	3.939	3.175
All	N	29	37	32	37	45
	MEAN	5.924	3.278	1.996	1.806	-1.979
	SD	3.427	4.050	3.424	4.116	3.602

Comments: Note that there is a discrepancy between the numbers (N) of patients at the top of the table and the Ns that appear in each patient treatment group at week 104. This discrepancy is confusing and potentially misleading. As noted in my comments above, there is a lack of clarity over the population that contributed the data for analysis. In the evaluation plan (*vide supra*), the sponsor states that the efficacy data will be derived from the ITT popuiation. The ITT population is clearly defined as those randomized patients who had both a baseline and at least one post-baseline evaluation. In contrast, the summaries of data that support efficacy at 104 weeks (presented in this table and in the following figures and tables) are not derived from the total defined ITT population of 239 patients, but are, in fact, based on results from the subset of completers

(approximately 186 patients). The efficacy of Vivelle, based on data taken from the entire randomized population, is calculated separately in the statistical review. The results of this analysis are essentially the same as for the completers analysis. However, the sponsor's claims for efficacy cannot be based on an ITT analysis of 239 patients (more on this below).

In the higher dose (0.1 mg and 0.05 mg) treatment groups, the increases in spinal BMD were about 3-6% over the course of 2 years, which is consistent with effects of HRT. The 0.0375 mg and 0.025 mg dose groups gained about 2% from baseline. This is somewhat lower, but represents a placebo-subtracted difference of about 4%.

I have summarized the pairwise comparisons (treatment vs placebo) at week 104 as follows (summary data derived from NDA submission):

% BMD change from baseline	Vivelle 0.1 mg vs placebo	0.05 mg vs placebo	0.0375 mg vs placebo	0.025 mg vs placebo
mean	8.65	5.14	3.41	3.76
95% CI	(5.93, 11.36)	(2.38, 7.90)	(0.33, 6.49)	(1.09, 6.43)
p	<0.001	<0.001	<0.024	<0.002

These data show that all 4 doses of Vivelle produced mean increases in spinal BMD that were statistically significantly different from the mean for the placebo group. Thus the primary efficacy outcome was achieved for the completer population. However, the between-dose treatment group differences were significant only for the 0.1 mg compared to each of the 3 lower doses. The pairwise differences between effects of each of the 3 lower doses were not statistically significant. I have summarized all the pairwise comparisons in the following table:

Other analyses:

Within-treatment group analysis:

The sponsor also conducted a within-treatment group analysis to determine whether the % change from baseline in AP lumbar spine BMD at week 104 is different from zero for each group. This analysis resulted in p-values of <0.001, <0.001, 0.002, and 0.011 for the Vivelle 0.1 mg/day, 0.05 mg/day, 0.0375 mg/day, and 0.025 mg/day treatment groups, respectively. For the placebo group, the same statistical test yielded a p-value of <0.001. However, as shown above, the mean for the placebo group was negative, while the means for all Vivelle dose groups were positive.

Effect of MPA status on primary efficacy outcome:

For the 3 higher doses of Vivelle (Vivelle 0.1 mg/day, Vivelle 0.05 mg/day, and Vivelle 0.0375 mg/day), the mean increases in spinal BMD at Week 104 were numerically greater for patients receiving concomitant MPA than for those who did not take a progestational agent. However, the order was reversed for Vivelle 0.025 mg/day and placebo. However, the number of patients treated with MPA was small (6-19 per treatment group Week 104), and the study lacked statistical power to compare the BMD differences between patients who were and who were not treated with MPA.

Summary statistics by menopause type: Similarly, only 18% of the patients (4-8 per treatment group at Week 104) had a surgical menopause, and there was insufficient statistical power to compare the surgical menopause group with the natural menopause group, in terms of BMD changes.

Summary statistics by center: The sponsor also has provided summary statistics for spinal BMD by center and visit. For each study center and visit, the Vivelle treatment groups showed an increase in spinal BMD compared to baseline, while the placebo group showed a decrease. This is consistent with the results obtained when data were pooled across all centers.

8.1.3.2 Secondary efficacy endpoints:

A listing of all secondary efficacy endpoints appears above in **8.1.1.4.1**. The following is a summary of results related to these endpoints.

BMD of the AP lumbar spine at Visits 4, 5, and 6 (26, 52, and 78 weeks):

At 52 and 78 weeks, each of the 4 Vivelle doses were associated with mean BMDs that were significantly greater than in the placebo group. At 26 weeks, the mean BMD for the 0.05 dose group was not significantly different from that in the placebo group, but the other 3 dose groups had mean BMDs that differed

significantly from placebo. I have summarized the results of this analysis in the following table:

MEAN ANTERO-POSTERIOR LUMBAR SPINE BMD BY TREATMENT GROUP AND TIME POINT: PAIRWISE COMPARISON WITH PLACEBO GROUP*.

Time post Rx (weeks)	Vivelle 0.1mg vs placebo	0.05 mg vs placebo	0.0375 mg vs placebo	0.025 mg vs placebo
26	3.67, p<0.001	1.42, p<0.97	2.19, p<0.006	1.72, p<0.015
52	6.98, p<0.001	4.55, p<0.001	3.98, p<0.001	3.02, p<0.001
78	8.27, p<0.001	5.36, p<0.001	4.88, p<0.001	3.83, p<0.001
104	8.65, p<0.001	5.14, p<0.001	3.41, p<0.024	3.76, p<0.002

* I have provided p-values only. The sponsor has also provided 95% CIs; these are consistent with the above, in terms of indication of statistical significance.

Comments: The data demonstrate (with one exceptional data point) a consistent, statistically significant increase in spinal BMD across all doses of Vivelle and at all time points, compared to placebo. This is important because of some concern that the lowest Vivelle dose may not be effective.

In keeping with comments above, it should be observed that the numbers of patients included in the efficacy analysis differ at each time point, because of dropouts from the trial. This is discussed further in the analysis of the femoral neck data.

Between-dose comparisons over time: The sponsor also presents pairwise comparisons between doses of Vivelle, at the same time points (Visits 4, 5, 6, and 7). This analysis shows that Vivelle, 0.10 mg/day, was significantly different, in terms of spinal BMD changes, from the 3 other doses at Visits 5 and 6 (Weeks 52 and 78), as was the case for Visit 7 (104 weeks). However, there were no significant differences among the 3 lower Vivelle doses at any observational time point during the trial. The only difference in the results for Visit 4, from the results at other visits, was that the Vivelle 0.1 mg/day dose was not significantly different from the Vivelle 0.0375 mg/day dose (p-value = 0.050). The sponsor provides a (NDA Appendix 5, Figures 1.35a-1.35d) display of linear dose relationships, showing a positive slope at Weeks 26, 52, 78 and 104 (each p-value <0.001).

Comments: It is clear from the data that, in terms of spinal BMD changes, all Vivelle doses are superior to placebo throughout the trial, that the Vivelle 0.1 mg /day dose is superior to all other doses, and that there are no consistent differences among the 3 lower doses.

Other secondary bone mineral endpoints (lateral lumbar spine BMD, femoral neck BMD, and total body BMC):

The sponsor provides a detailed analysis of the pairwise comparisons (comparisons between effects of each dose with placebo, as well as comparisons between doses) for these secondary efficacy variables at Visits 4, 5, 6, and 7. These results are summarized here.

The % changes from baseline in femoral neck BMD and total body BMC at Visit 7 (Week 104) were consistent with those of the primary efficacy variable: all doses of Vivelle were statistically significantly superior to placebo (where there were consistent losses of about 2-3%). For lateral lumbar spine BMD, the 3 dose groups of Vivelle were not statistically different from placebo at Week 104. However, the Vivelle 0.1 mg/day dose group showed a significant difference from placebo (p= 0.023).

I have summarized these results in the following table (data integrated across several of the sponsor's statistical summary tables). The numbers represent least mean squares of % changes in BMD or BMC from baseline to Week 104. P-values relate to significance of pairwise comparisons with placebo.

BMD AND BMC CHANGES (AS % OF BASELINE) ASSOCIATED WITH 4 DOSES OF VIVELLE, COMPARED WITH PLACEBO, AT 104 WEEKS

% Change from baseline (LS means)to Week 104 in:	Vivelle 0.10 mg N=42	Vivelle 0.05 mg N=48	Vivelle 0.0375 mg N=41	Vivelle 0.025 mg N=47	Placebo N=61
Lateral lumbar spine L1-L4 BMD	4.25, p=0.023	2.89, p=0.140	2.71, p=0.168	2.02, p=8.18	- 2.17
Femoral neck BMD	2.98, p<0.001	0.10, p=0.037	0.47, p=0.037	-0.08, p=0.044	- 2.99
Total Body BMC	2.88, p<0.001	1.76, p<0.001	1.07, p<0.001	0.12, p=0.003	- 2.99

Comments: As noted above, the Ns that are given by the sponsor do not represent the number of patients from whom the data were derived. Rather, these represent the numbers of patients who fit the data for the ITT population (N=239). For the femoral neck, examination of the sponsor's

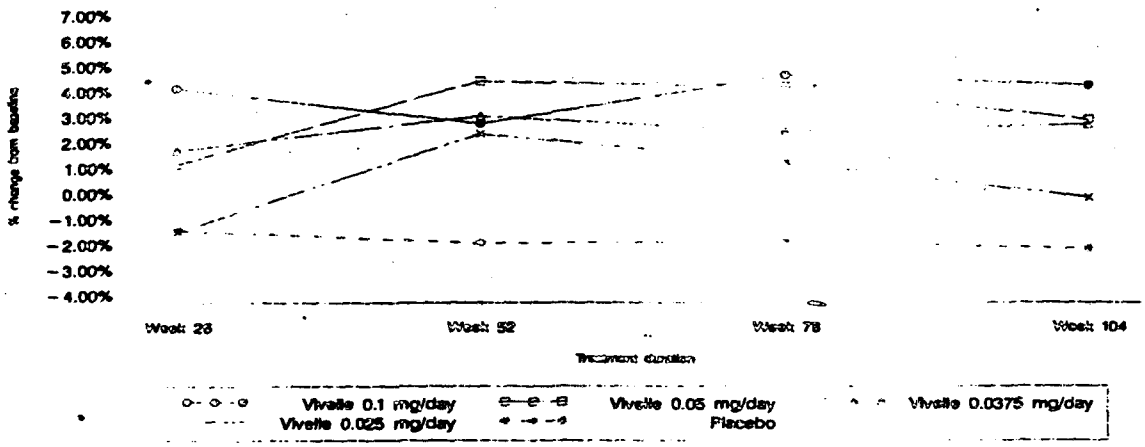
post-text table 9.2-7 reveals that the numbers of patients in the 5 analytical groups were 29, 37, 32, 37, and 46 for the 0.1, 0.050, 0.0375, 0.025, and placebo, respectively. The total analyzed was 181, not 239.

Changes at Weeks 26, 52, and 78:

The changes in these secondary endpoints during the course of the trial are depicted graphically in the next 3 figures. At all 3 of the intermediate time points, Vivelle, 0.10 mg/day, was superior to placebo at the lateral lumbar spine and femoral neck. However the analysis of data for the 3 other dose groups yielded a mixture of significant and non-significant differences when compared to placebo at these time points. In addition, there were generally no statistically significant differences among the Vivelle doses at these 3 time points.

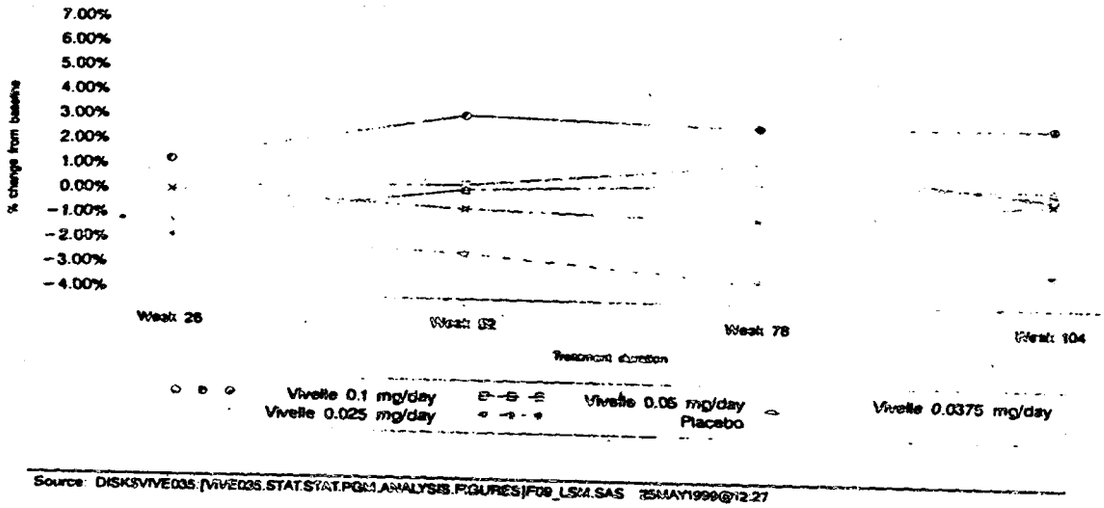
Total body BMC was measured at baseline and at 52 and 104 weeks (Visits 5 and 7). The results for Visit 7 are depicted above: the mean BMC values for all 4 dose groups were significantly greater than in placebo at this time point. At Visit 5 (52 weeks), all Vivelle doses with the exception of 0.0375 mg/day, were associated with statistically significantly greater BMC measurements than were found in the placebo group (the 0.0375 mg group BMC was numerically greater than placebo). The between-Vivelle-dose comparisons were, in general, not significant at Visit 5 for BMC.

Figure 9.2-1
Bone mineral density – lateral lumbar spine (L2-L4)
Least squares means of percent change from baseline versus treatment duration
(All intent-to-treat patients)



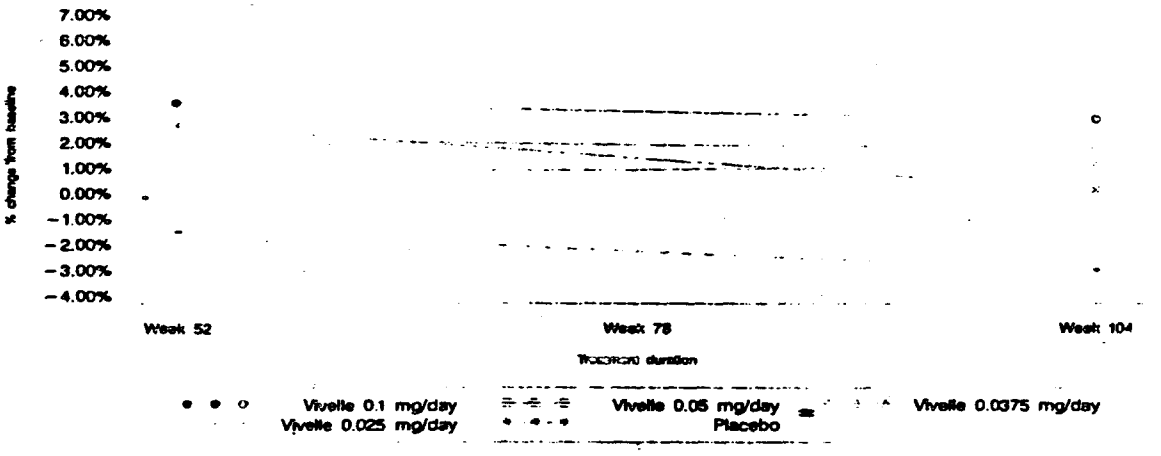
Source: DISK3VIVE035:[VIVE035.STAT.STAT.PGM.ANALYSIS.FIGURES]F09_LSM.SAS 25MAY1999@12:27

Figure 9.2-2
Bone mineral density – femoral neck
Least squares means of percent change from baseline versus treatment duration
(All intent-to-treat patients)



Source: DISK8\VIVE035.[VIVE035.STAT.STAT.PGM.ANALYSIS.FIGURES]F09_LSM.SAS 25MAY1999@12:27

Figure 9.2-3
Whole body bone mineral content
Least squares means of percent change from baseline versus treatment duration
(All intent-to-treat patients)



Source: DISK$VIVE035:[VIVE035.STAT.STAT.PGM.ANALYSIS.FIGURES]F09_LSM.SAS 25-MAY1999@12:27

Comments: Again, the labeling of these figures as "all intent-to-treat patients" is misleading.

Serum osteocalcin and urinary NTx /creatinine ratio:

Changes in these two bone turnover markers constituted the final set of secondary endpoint measurements. In states of estrogen deficiency, bone turnover rates increase. These are followed by increases in rates of bone formation, since the two processes are physiologically coupled. The increases in bone formation never completely compensate for increases in bone resorption, however. As a consequence, there is net loss of bone mineral. Treatment with anti-resorptive agents, such as bisphosphonates or estrogen, are known to decrease the rate of bone turnover. As a reflection of this, the markers of bone resorption (e.g., NTx) and bone formation (e.g., osteocalcin), generally decline, often into the premenopausal range.

The sponsor has presented the bone marker data in detail in a series of tables (9.2-13 to 9.2-18) and in two figures. There was an overall tendency towards a decline in bone markers in treated groups and a tendency towards no change or increase in placebo at most time points. However, this study failed to demonstrate consistent, statistically significant results in either Vivelle vs placebo comparisons, or between Vivelle dose comparisons at Weeks 13, 26, 52, 78, or 104. At Week 104, the serum osteocalcin decreased numerically from baseline in the Vivelle 0.1 mg/day, 0.05 mg/day, and 0.025 mg/day treatment groups, but increased in the 0.0375 mg/day and placebo groups. The urinary NTx/creatinine ratio decreased from baseline to Visit 7 (Week 104) in the Vivelle 0.1 mg/day, 0.0375 mg/day, and 0.025 mg/day treatment groups, but increased in the Vivelle 0.05 mg/day and placebo groups.

The sponsor's figure, reproduced below, depicts changes in NTx/creatinine in all treatment arms throughout the trial.

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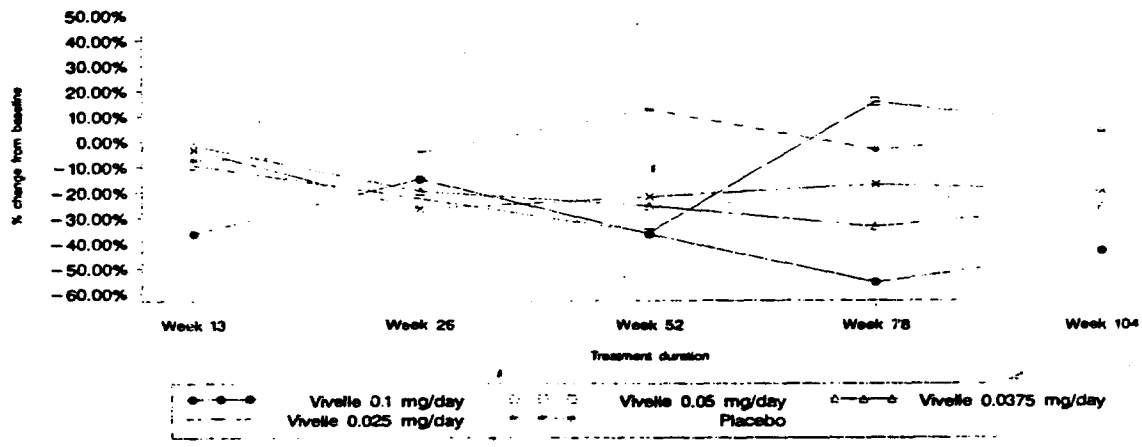
Figure 9.2-5
Urinary NTx creatinine ratio
Least squares means of percent change from baseline versus treatment duration
(All intent-to-treat patients)



Source: DISK$VIVE035:[VIVE035.STAT.STAT.PGM.ANALYSIS.FIGURES]F09_LSM.SAS 25MAY1999@12:27

Comments: These results are disappointing, but not surprising, given the variability of endogenous bone marker levels as measured with these assays, as well as the small numbers of patients in each treatment arm. The patients' age and proximity to menopause may also have played a role in these outcomes. It is interesting to compare these results with those of larger osteoporosis studies in somewhat older women, in which statistically significant declines in marker levels have been observed with bisphosphonate or estrogen therapy.

Other analyses:

The sponsor also conducted an exploratory analysis of the correlation between bone markers and bone loss. This study assessed the correlation between the

change from baseline in bone turnover markers at Weeks 13, 26, 52, 78, and 104 and AP spinal BMD changes from baseline to Week 104. There was no strong correlation between the variables (figures 9.2-6 to 9.2-15 of the NDA submission).

Comments: Again, this is not surprising, given the above considerations, plus the fact that this was an attempt to correlate changes among three surrogate markers.

Height: The sponsor measured patients' height at baseline and at Week 104. The summary statistics for this measurement appear in table 10.4-5 of the NDA application. There was no measurable change in height in any of the treatment dose groups or in the placebo group over the 2-year period.

Comments: Loss of height is an important clinical consequence of spinal osteoporosis, although there are non-osseous causes as well (e.g., inter-vertebral disk herniation). Maintenance of stature is one reason to prevent or treat this disease, and height should be measured as part of every large osteoporosis trial.

It is interesting that in all large phase 3 trials of alendronate in postmenopausal osteoporosis, [redacted] all treatment groups demonstrated a steady loss of height during the 3 or 4 years of the studies. The loss of height was about 2-3 mm/year for the placebo groups and about 1-1.5 mm less for alendronate-treated patients. As noted in my earlier reviews of alendronate, the inexorable loss of height in most groups of bisphosphonate-treated postmenopausal women occurs despite substantial increases in mean spinal BMD and greater than 90% positive responder rates.

In the present study of Vivelle, it is most probable that the lack of change in stature in the placebo group was due to the relative youth of the trial population. On the other hand, it is worth noting that a previous study of effects of HRT with and without alendronate, showed that estrogen treatment conferred no advantage over placebo, in stature changes after two years of treatment. Thus the effects of estrogen replacement therapy on height loss remain to be determined.

8.1.2.3 Safety outcomes

The sponsor has provided extensive safety results, evaluated by individual variable and by treatment group. Individual patient data listings are provided in the Appendix of the NDA. This review will focus on AEs that are known to be

associated with estrogen use. In addition, unanticipated AEs will be described, and all serious AE's will be reviewed and discussed in detail[3].

Safety population and nature of safety data: The safety population for this trial (trial # 035) consisted of all patients treated with at least one application of the trial drug and who had at least one post baseline safety evaluation (N=259). The frequency of AEs, by body system and treatment group, are presented in tabular form in the NDA application. The sponsor lists all AEs, whether or not they were judged by the investigators to be drug-related. AEs that were considered to be drug-related are also listed separately in the NDA.

AEs in general: Examination of the tables reveals that 83.7-93.9% of all patients in each of the 5 treatment groups (including placebo) reported one or more AEs. The number of patients reporting one or more AEs did not differ significantly across the 5 groups.

In the active treatment groups, the most frequently reported AEs were in the reproductive system, followed by gastrointestinal and musculoskeletal systems. In the placebo group, the most frequently reported AEs were in the respiratory system followed by musculoskeletal and gastrointestinal systems.

All AEs related to the reproductive system: These were reported significantly more frequently in Vivelle treated patients than placebo patients (53.1% in the 0.1 mg group, 34.0% in the 0.05 group, 46.5% in the 0.0375 mg group, and 31.9% in the 0.025 mg group, compared with 19.4% of patients in the placebo group.

I have summarized reproductive system disorders, exclusive of neoplasms, by dose in the next table. These are AE's that occurred with a frequency of 5% or greater, in at least one treatment arm. They are listed regardless of whether they were judged to be trial drug related. In this table, have abstracted data from the sponsor's summary listings and included all symptoms related to the GU system. Numbers refer to individual patients; percentages are in parentheses.

[3] Following the safety review of this study, I will summarize an integrated safety summary of all Vivelle studies, together with a 120 day safety update for Vivelle and safety data on Menorest.

ADVERSE EVENT	VIVELLE 0.1 MG N=49	0.05 MG N=53	0.0375 MG N=43	0.025 MG N=47	PLACEBO N=67
Genital disorder	2 (4.1)	5 (9.4)	2 (4.7)	1 (2.1)	1 (1.5)
Inter-menstrual bleeding	11 (22.4)	5 (9.4)	8 (18.6)	1 (2.1)	3 (4.5)
Breast pain	15 (30.6)	9 (17.0)	10 (23.3)	8 (17.0)	2 (3.0)
Spotting, vaginal	4 (8.2)	3 (5.7)	5 (11.6)	3 (6.4)	4 (6.0)
Vaginitis	3 (6.1)	1 (1.9)	1 (2.3)	0	1 (1.5)
Moniliasis	2 (4.1)	0	3 (7.0)	2 (4.3)	0
Urinary tract infection	1 (2.0)	0	4 (9.3)	1 (2.1)	2 (3.0)

Neoplasms of the reproductive system: I have summarized the category, "neoplasms of the reproductive system" in the next table (numbers in parentheses refer to numbers of patients with neoplasm):

VIVELLE DOSE	REPRODUCTIVE SYSTEM NEOPLASM
0.1 mg	nodular density, breast (1); fibrocystic breast (1); breast lump (1); breast cyst (1); uterine fibroid (1) cervical polyp (1)
0.05 mg	none
0.0375 mg	breast lump (1); breast nodules around nipple (1)
0.025 mg	uterine fibroid (1)
PLACEBO	breast cyst and fibroadenosis (1); cervical polyp (1); ovarian cyst (1)

Note that the 12 patients identified in the above table represent 12 distinct individuals.

Also, AEs reported under "neoplasms of body as a whole" were: lipoma in two patients treated with Vivelle 0.0375 mg/day and right adnexal mass (preferred

term "neoplasm nonspecific") in one Vivelle 0.1 mg/day treated patient who is discussed further below.

Other AEs known to be associated with estrogen use:

I have abstracted, from the sponsor's data, all other AEs that are known to be associated with estrogen use or with hypoestrogenism. These AEs occurred with a frequency of 5% or greater in any arm of the study.

ADVERSE EVENT	VIVELLE 0.1 MG N=49	0.05 MG N=53	0.0375 MG N=43	0.025 MG N=47	PLACEBO N=67
edema	3 (6.1)	0	1 (2.3)	2 (4.3)	2 (3.0)
Weight increase	1 (2.0)	1 (1.9)	5 (11.6)	4 (8.5)	2 (3.0)
migraine	1 (2.0)	1 (1.9)	5 (11.6)	1 (2.1)	2 (3.0)
fracture	3 (6.1)	1 (1.9)	0	3 (6.4)	1 (1.5)
All psychiatric disorders*	2 (4)	10 (19)	9 (21)	12 (26)	16 (24)
Hot flushes	1 (2.0)	3 (5.7)	1 (2.3)	3 (6.4)	6 (9.0)
hypertension	1 (2.0)	3 (5.7)	1 (2.3)	2 (4.3)	2 (3.0)

• Pooled reports of depression, anxiety, and insomnia

Local application site reactions:

I have summarized application site reactions, by treatment group, as follows:

Vivelle 0.1 mg	0.05 mg	0.0375 mg	0.025 mg	Placebo
4 (8.2%)	6 (11.3%)	3 (7.0%)	3 (6.4%)	6 (9.0%)

These consisted of patch site erythema, itching, rash, burning, and irritation.

Comments: The adverse events listed above are within expectations for a trial of HRT in this age group, in terms of nature, frequency and dose assignment. Note, however, that these figures represent categories for which the frequencies of reports exceeded 5%. All individual AE's that are

known to be associated with estrogen use and that were severe are identified in the next section.

Intensity of AE's by treatment group:

The sponsor summarizes the severity of AEs, whether or not trial drug-related, in the following table:

Table 10.1-5 Summary of severity of AEs – whether or not trial drug-related (all safety patients)

	Number (%) of patients with AE		
Treatment Group	**Mild**	**Moderate**	**Severe**
Vivelle 0.1 mg/day	11 (22.4%)	31 (63.3%)	4 (8.2%)
Vivelle 0.05 mg/day	24 (45.3%)	23 (43.4%)	3 (5.7%)
Vivelle 0.0375 mg/day	15 (34.9%)	15 (34.9%)	6 (14.0%)
Vivelle 0.025 mg/day	11 (23.4%)	26 (55.3%)	6 (12.8%)
Placebo	14 (20.9%)	33 (49.3%)	10 (14.9%)

Source: Post-text table 10.1-3

Comments: The frequency distributions appear relatively stable across the 5 treatment arms. However, the information derived from this analysis is limited.

I have summarized all the significant and serious adverse events in the following table.

Note that there were no deaths.

SIGNIFICANT AND SERIOUS ADVERSE EVENTS, BY TREATMENT GROUP

Event	Vivelle 0.10 mg	0.05 mg	0.0375 mg	0.025 mg	Placebo
All non-fatal SAEs, plus other significant AEs	4 (8%)	4 (7.6%)	4 (9.3%)	5 (10.7%)	6 (9.0%)
Any AE causing dis-continuation	12 (24.5%)	5 (9.4%)	4 (9.3%)	4 (8.5%)	2 (3.0%)

Comment: Further examination the sponsor's individual listing of events leading to discontinuation shows that 7 of the 12 patients in the 0.10 mg group discontinued due to vaginal bleeding and one for breast tenderness. Overall, vaginal bleeding was the commonest reason for discontinuation in the active treatment groups.

Severe AEs were reported in a total of 13 patients. I have summarized these as follows:

Vivelle 0.10 mg	A) stabbing headache B) cellulitis of leg C) acute MI
0.05 mg	A) acute gastroenteritis
0.0375 mg	A) pyelonephritis B) herniated lumbar disc C) flu syndrome
0.025 mg	A) deep vein thrombosis B) herniated lumbar disc
Placebo	A) 2 patients with chest pain B) hypertension/migraine C) elective breast reduction surgery

Clinical details for these cases are provided by the sponsor (post-text supplement 2). Of greatest concern are the myocardial infarction, the DVT, and the cellulitis followed by DVT. The patient with the cellulitis followed by DVT was a 58-year-old woman, weight 150 lbs, with no prior history of either disorder. Approximately 5 months after starting Vivelle, 0.1 mg/day, she was hospitalized with fever, chills, and swelling of the right leg. PE showed erythema with pitting edema of the right leg. The rest of the workup was negative (Doppler negative). She was treated with antibiotics for 3 weeks and recovered completely. Apparently, the diagnosis was cellulitis. One year later, while still in the trial and on the medication, she was reported to have a DVT by the investigator (details not supplied) and was discontinued from the trial.

The patient with the MI was a 59-year old woman with no history of heart disorder. Approximately 5 months after starting Vivelle, 0.10 mg, she presented to an emergency room with chest pain, radiating to throat and both arms. She was diagnosed with acute MI and had an angioplasty with a stent. She recovered completely and was not discontinued from the trial.

The patient with the DVT was a 51-year-old woman, weight 180 lbs, who had been taking Vivelle 0.025 mg for 13 months. Her medical history includes a history of DVT 30 years prior to the trial, during pregnancy. During the trial, she was hospitalized for DVT of left leg, confirmed by ultrasound. She was treated with heparin and coumadin, recovered, and was discontinued from the trial.

Comments: In the opinion of the investigator, the DVT was probably trial drug-related. I concur. In the opinion of the investigator, there was no relationship between trial drug and the MI. It is impossible to make an independent judgment about this. There is insufficient information on the patient with cellulitis followed by DVT to make an independent judgment. However, the association of DVT with higher estrogen doses makes the event likely to be drug-related, in my opinion.

Laboratory safety outcomes:

Hematology, serum chemistry, and urinalyses were performed at baseline, at Week 52, and at Week 104; or, for those patients who terminated prematurely, at discontinuation. Parameters that were followed included mean changes from baseline, shift from baseline in number of patients with laboratory values outside of specified ranges, and assessment of clinical significance of abnormal laboratory values or values outside of specified ranges.

For changes from baseline in mean laboratory values, there were no significant changes in hematology or chemistry values. For hematology, this included hemoglobin, hematocrit, rbc, wbc plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet counts. For serum chemistries, values included BUN, creatinine, ALT, AST, total bilirubin, alkaline phosphatase, glucose, total cholesterol, alpha1 HDL cholesterol, LDL cholesterol, triglycerides, total calcium, phosphorus, and TBG. Complete details are included in tabular form in the NDA.

Of interest, the sponsor presents changes in serum lipids over time in the following table:

Mean change from baseline in serum lipids by treatment group and visit

	Visit 5 (Week 52)			Visit 7 (Week 104)		
Test Treatment group	**N**	**Baseline**	**Change from baseline**	**N**	**Baseline**	**Change from baseline**
Total cholesterol (mg/dL)						
Vivelle 0.1 mg/day	35	228.8	-17.1	31	231.2	-5.0
Vivelle 0.05 mg/day	45	219.0	4.4	40	220.2	4.2
Vivelle 0.0375 mg/day	39	231.0	-6.4	32	232.2	-2.9
Vivelle 0.025 mg/day	41	233.6	-2.1	36	231.3	11.1
Placebo	55	220.8	-5.0	45	216.5	10.7
Alpha1 HDL cholesterol (mg/dL)						
Vivelle 0.1 mg/day	35	55.5	-1.8	31	55.7	-0.8
Vivelle 0.05 mg/day	45	58.1	0.3	40	58.2	-1.1
Vivelle 0.0375 mg/day	39	64.1	-0.5	32	65.0	-0.4
Vivelle 0.025 mg/day	41	65.8	-1.1	36	64.8	-1.8
Placebo	55	64.0	-0.5	45	65.0	0.7
LDL cholesterol (mg/dL)						
Vivelle 0.1 mg/day	32	138.5	-11.8	29	140.9	-2.3
Vivelle 0.05 mg/day	44	134.9	0.5	39	135.7	3.6
Vivelle 0.0375 mg/day	37	140.5	-1.3	31	141.3	0.9
Vivelle 0.025 mg/day	40	145.1	-3.1	36	144.1	11.4
Placebo	55	132.3	-4.7	45	128.0	8.7
Triglycerides (mg/dL)						
Vivelle 0.1 mg/day	35	171.2	-7.6	31	170.6	-10.9
Vivelle 0.05 mg/day	45	131.6	15.9	40	133.0	7.9
Vivelle 0.0375 mg/day	39	143.6	-24.8	32	137.2	-17.5
Vivelle 0.025 mg/day	41	116.3	8.9	36	112.7	7.3
Placebo	55	122.5	0.7	45	117.6	6.0

Source: Post-text tables 10.1-1, 10.1-2

Comments: There are no consistent Vivelle-related changes in any of these parameters throughout the trial. There is no obvious explanation for some of the dose-specific changes in total cholesterol and triglycerides, aside from the effects of chance on the analysis of multiple endpoints.

Laboratory values

Analysis of number of patients with shifts from baseline:

The number of patients with laboratory value shifts from normal (at baseline) to abnormal post-baseline were similar across all 5 treatment arms. In the following table, the sponsor presents shift frequencies for which ≥ 5% patients in any of the treatment group had such changes:

Table 10.3-2 Summary of frequently occurring shifts (≥ 5% patients in any treatment group) from normal at baseline to abnormal post-baseline value (monitor specified ranges)‡ by laboratory test and treatment group

	Percent patients with shift				
Laboratory test	Vivelle 0.1 mg/day	Vivelle 0.05 mg/day	Vivelle 0.0375 mg/day	Vivelle 0.025 mg/day	Placebo
Hematology					
Monocytes, low (<4%)	14.0	12.8	10.0	16.7	16.7
Serum chemistry					
SGPT/ALT, high (>44 U/L)	9.3	6.3	7.5	4.8	11.7
Alkaline phosphatase, high (>213 U/L)‡	4.7	2.1	7.5	2.4	6.7
SGOT/AST, high (>46 U/L)	7.0	0	2.5	0	6.7
Creatinine, high (>1.1 mg/dL)	7.0	4.2	12.5	11.9	10.0
Triglycerides, high (>210 mg/dL)	11.6	18.8	5.0	11.9	8.3
Cholesterol LDL, high (>197 mg/dL)	4.9	2.1	2.6	4.8	6.7
Low (<131 mg/dL)	24.4	17.0	15.8	9.5	13.3
Thyroxine binding globulin, low (<1.2 mg/dL)	2.3	2.1	5.0	0	0
Urinalysis					
Hemoglobin, high (>0)	16.7	10.4	10.0	4.9	10.3

Source: Post-text table 10.3-5; Data listing 10.3-2 ‡ Age dependent.

Clinically significant laboratory abnormalities: These are listed individually in the NDA (Appendix 7, Data listings 10.3-7 and 10.3-8).

Laboratory abnormalities were reported as an AE in three patients who were receiving Vivelle (hypercholesterolemia, hypokalemia, and pyelonephritis). None of these was considered to be trial drug-related.

In addition, 7 patients had laboratory abnormalities that were considered by the investigator as clinically significant and/or trial drug-related. These were:

A transient elevation ALT (30 to 159 U/L), and AST (28 to 98 U/L) at Week 52 in one Vivelle 0.1 mg/day treated patient; these tests returned to baseline level at Visit 7 (Week 104).

Elevated AST and alkaline phosphatase in one Vivelle 0.1 mg/day treated patient was considered to be related to alcoholism and cirrhosis. AST increased from 37 U/L at baseline to 102 and 155 U/L and serum alkaline phosphatase increased from 245 mg/dL at baseline to 270 mg/dL and 615 mg/dL at Week 52 and Week 104, respectively.

Elevation of ALT 38 U/L at baseline, 54 and 62 U/L at Weeks 52 and 104 in a Vivelle 0.05 mg/day treated patient; this was attributed to known chronic alcohol abuse.

Elevation of alkaline phosphatase (263 at baseline to 291 and 314 at Weeks 52 and 104) was observed in one Vivelle 0.0375 mg/day patient. This was judged unrelated to study drug.

Elevation of AST (21 U/L to 90 U/L) and ALT (22 U/L to 132 U/L) in one placebo treated patient was thought to be related to recent viral illness.

Elevation of ALT (43 U/L to 83 U/L) at 78 weeks in one placebo patient was thought to be drug-related, but not clinically significant.

Reduced hemoglobin and hematocrit at Week 52 (9.9 g/dL and 29.8%, respectively) in one placebo patient was attributed to blood donation six days prior to the blood test.

Comments: None of these results is clearly related to estrogen use or is indicative of hazard in association with estrogen in the absence of other risk factors (e.g., alcohol abuse).

Vital signs

The sponsor presents summary statistics for change from baseline in systolic and diastolic BP, HR, and weight, by visit and treatment group (tables 10.4-1 through 10.4-4). According to these summary data, there were no clinically significant changes from baseline in these parameters in any of the treatment groups. Limits were: mean systolic blood pressure, (≤ 6.5 mmHg increase, ≤ 2.6 mmHg decrease), diastolic blood pressure (≤ 4.5 mmHg increase, ≤ 4.1 mmHg decrease), pulse (≤ 2.5 bpm increase, ≤ 3.7 bpm decrease) or weight (≤ 3.6 kg increase) in any of the treatment groups.

Individual patients with clinically notable vital signs are summarized in the NDA. There were four patients (one Vivelle 0.1 mg, two Vivelle 0.025 mg, and one placebo) with decreased systolic blood pressure (78 to 86 mmHg, decrease of 20 mmHg or more) at one or two visits. One patient (Vivelle 0.025 mg) had an increase in systolic blood pressure from 162 mmHg at baseline to 186 mmHg at one of the visits. There were no associated significant changes in diastolic BP in any of these patients.

Other safety evaluations

The sponsor performed additional safety evaluations that are relevant to a study of HRT. These included post-treatment physical and gynecological examinations, endometrial biopsy, endometrial bleeding assessment, and mammography.

Gynecological examination:

The sponsor presents a summary of gynecological examination results tables 10.5-1 to 10.5-10 of the NDA. Clinically significant abnormalities were reported at post-treatment in four patients (one Vivelle 0.1 mg and three placebo patients): right breast lump in upper outer quadrant (Vivelle 0.1 mg) red, maple syrup color discharge on left breast nipple (placebo) bilateral ovarian cyst on sonogram (placebo), and palpable ovaries (placebo, sonogram report not available).

All of the above findings, except the last, were reported as AEs.

Endometrial biopsy:

A baseline endometrial biopsy was performed in 97 of 100 nonhysterectomized patients; a post-treatment biopsy was performed in 73 patients. There were no reports of endometrial hyperplasia in any of the treatment groups at pre- or post-treatment evaluation.

Other findings at the post-treatment evaluation: atrophic endometrium (13 active treatment groups, 6 placebo); weakly proliferative (12 active treatment groups, 3 placebo). Insufficient tissue was reported in 14 patients (10 active treatment groups, 4 placebo). Proliferative endometrium was found in 4 active treatment patients; an endometrial polyp was reported in one Vivelle treated patient. Inactive endometrium was found in 7 active treatment patients and 4 placebo); benign glandular tissue in 4 active treatment and 2 placebo patients; and bleeding pattern or menstruating endometrium in 2 active treatment patients.
Vaginal bleeding assessment:

Vaginal bleeding (clinical) assessment:

The sponsor presents a summary of vaginal bleeding assessment by treatment group and visit in NDA table 10.5-14, together with a listing of patients reporting abnormal vaginal bleeding (Data listing 10.5-3). In addition, any abnormal vaginal bleeding was reported as an AE, indicating spotting or bleeding.

In the following table, I have summarized the sponsor's data on abnormal vaginal bleeding:

ABNORMAL VAGINAL BLEEDING IN ALL NON-HYSTERECTOMIZED SAFETY PATIENTS, BY TREATMENT

ABNORMAL VAGINAL BLEEDING	VIVELLE 0.10 MG N=17	0.05 MG N=20	0.0375 MG N=19	0.025 MG N=20	PLACEBO N=24
YES	14 (82.4%)	6 (30%)	9 (47.4%)	3 (15%)	6 (25%)
NO	3 (17.6%)	14 (70%)	10 (52.6%)	17 (85.0%)	18 (75%)

Comments: Once again, there is evidence for a more potent estrogenic effect in the Vivelle 0.10 mg group, compared to the 3 lower doses as well as placebo.

Mammography:

Baseline mammography, performed on all safety patients (N=259), showed no clinically significant abnormalities. At the post-treatment evaluations 3 Vivelle 0.1mg and 2 Vivelle 0.0375 mg patients had the following abnormalities:

In the Vivelle, 0.1 mg group:

1) A 52 year old patient with a small cyst, considered to be trial drug related.
2) A 45 year old with altered parenchymal pattern and dense fibroglandular tissue, thought to be estrogen related
3) A 53 year old with fibrocystic changes in both breasts and a retroareolar nodule.

In the Vivelle, 0.0375 mg group:

1) A 27 year old with a well-marginated, noncalcified asymmetric density in right breast, thought to represent a benign lymph node at Week 52. The finding disappeared at Week q0e.
2) A 46 year old found to have one or two densities at Week 52. No abnormalities were found at Week 104.

Papanicolaou test:

No clinically significant abnormality was found in any of the patients at baseline or at any post treatment evaluation, with one exception: A 51 year old treated with Vivelle 0.025 mg had atypical endocervical cells at Week 52. The repeat evaluation was normal. A repeat at Week 104 was normal.

Comments: These special safety studies were comprehensive and appropriate to a trial of HRT. The results show an expected increase in reproductive system AEs in association with active drug, particularly the higher doses. However, there are no surprising or alarming data in this study.

8.1.2.3.1 Other safety data

Other data relating to the safety of Vivelle and to Menorest are presented in the NDA. The sponsor has submitted an Integrated Summary of Safety (ISS), comprising data from four clinical trials. In addition, a listing of all phase 4 adverse events is provided, as well as a 120-day safety update. Finally, the sponsor has provided literature supporting the efficacy and safety of Menorest, an identical product.

The ISS integrates data from the present study (035) with those from 3 other trials of Vivelle and other estradiol patches in postmenopausal women (036, 037, and 038). The following table summarizes the number of patients and exposure times for the 3 studies:

STUDY #	OBJECTIVE	N AND DOSE	POPULATION	TREATMENT DURATION
036	PREVENTION OF VASOMOTOR SYMPTOMS	130 VIVELLE PATCH 0.0375 MG; 127 PLACEBO PATCH	POST-MENOPAUSAL WOMEN	12 WEEKS
037	ASSESS SKIN REACTIONS	210 WITHIN-PT. COMPARISON VIVELLE 0.05MG, CLIMARA 0.05MG, OR PLACEBO	SAME	22 DAYS
038	ASSESS SKIN REACTIONS	213 SAME AS ABOVE	SAME	22 DAYS

Thus these studies were far shorter than the present trial (035). The target populations were essentially the same as for 035. Patients in these studies were hysterectomized or non-hysterectomized. The safety data that were collected were essentially the same as in 035. Additionally, in 036, endometrial thickness was measured by transvaginal ultrasound at baseline and at the end of study treatment. In this study, a baseline endometrial biopsy was performed in all

patients with an intact uterus. Patients with endometrial thickness of > 4 mm at post-treatment evaluation underwent an additional endometrial biopsy.

In general, the adverse experiences found in these 3 trials were similar to those that were seen in 035. All AE's for these 3 trials are summarized in the sponsor's ISS.

Deaths and non-fatal SAEs:

There were no deaths in any of the studies.

The sponsor reports the following nonfatal serious adverse events:

Study 036

Two SAEs were reported during the course of this study. Both patients were receiving Vivelle and both were hospitalized for conditions that pre-dated the study, chronic obstructive pulmonary disease, and cholelithiasis

Study 037
There was one patient with a serious adverse experience. This patient had completed the treatment period and was hospitalized three days later for acute cholecystitis. The event was not considered related to trial treatment by the investigator.

Study 038

No serious adverse events occurred during this study.

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Discontinuations during the three studies:

Study 036

This was a 12-week study. The following table (sponsor's Table 13.6-1) shows a listing of the four patients who discontinued from 036 due to AEs:

Table 13.6-1. Discontinuations due to AEs (Study 036)

Center / Patient no	Treatment	Age	Adverse event(s) causing discontinuation	Investigator's assessment of relationship to drug
M0462I/222	Vivelle	68	Severe breast tenderness severe nipple swollen moderate fluid retention	probable
M0459H/128	placebo	52	Severe Insomnia	possible
M0459H/290	placebo	44	Severe insomnia vaginal dryness moderate irritability	possible
M0459H/386	placebo	44	Severe migraine headaches vaginal dryness intermittent insomnia emotional	possible, highly probable, probable, probable

Study 037

This was a shorter study (22 days). Six patients prematurely discontinued the trial due to non-serious AE's. All events were considered trial drug related by the investigator. These were: malaise, hot flashes and weakness for one patient, headache in two patients, irritation at the site of patch application in two patients and vaginal itching and dryness, mood changes, sleep disturbances, right ovarian cramping and bilateral nipple hardness.

No patients discontinued because of laboratory abnormalities.

Study 038

This study also was 22 days in duration. Three patients prematurely discontinued the trial due to non-serious AEs: one due to superficial phlebitis of the left leg, one due to bilateral breast and nipple tenderness, and one due to a burning sensation in the left medial back, depression, nervousness and left breast tenderness. All of these events were considered trial drug related by the investigator. They were attributed to HRT or to postmenopausal symptoms.

Vaginal bleeding and endometrial evaluations (Study 036)

Vaginal bleeding: Results of a vaginal bleeding assessment study, as part of 036, were similar to 035. Vaginal spotting (and/or bleeding) was reported by 12 of 34

(35.3%) nonhysterectomized Vivelle-treated patients and 5 of 25 (20%) nonhysterectomized placebo-treated patients.

Endometrial thickness:

On TVU, there was a greater increase in endometrial thickness from baseline in Vivelle-treated patients than in placebo, as shown in the sponsor's table below:

Table 13.10-1. Summary statistics for the change from baseline in endometrial thickness (mm) by treatment group (all intent-to-treat nonhysterectomized patients, Study 036)

	Vivelle			Placebo		
	Baseline (Visit 1)	Post (Visit 6)	Diff	Baseline (Visit 1)	Post (Visit 6)	Diff
N	33	33	33	25	25	25
Mean	3.1	5.8	2.7	3.2	3.8	0.5
SD	1.3	2.6	2.7	0.9	1.8	1.5
Median	3.0	6.5	3.0	3.0	3.7	1.0

Source: Data Listing VI-7.1-9 in the Study 036 report

Comments: These data are consistent with estrogen treatment.

Endometrial histology:

In this study, 22 of 34 (64.7%) nonhysterectomized Vivelle treated patients and 9 of 25 (36%) nonhysterectomized placebo-treated patients had endometrial thickness of > 4.0 mm following the trial treatment. Of these, the post-treatment biopsy showed simple hyperplasia in 2 Vivelle treated patients. Of interest, the post-treatment endometrial thickness in these 2 patients was 7.0 mm (baseline 2.0 mm) and 6.1 mm (baseline 1.8 mm). None of the placebo-treated patients were found to have endometrial hyperplasia.

Post-marketing experience with Vivelle—data submitted from the Novartis Safety Database:

During the post-marketing period (March, 1996-February 19, 1999) a total of 1064 spontaneous adverse event reports were received in association with Vivelle use.

No deaths were reported.

The most frequently reported adverse events were: application site reactions, breast tenderness, lack of efficacy (including hot flushes and night sweats), headache, and nausea. These are frequently reported in association with estrogen use or as part of the constellation of menopausal symptoms.

There were 8 serious AE's among these 1064 spontaneous reports. These are summarized in the next (sponsor's) table:

Table 15.2-1. Serious adverse events (spontaneous safety reports)

Case ID	SAE (Preferred Term)	Treatment group (Therapy Duration until serious adverse event)
98USA10380	Breast tissue changes Breast enlargement Uterine hemorrhage Neoplasm uterine	Vivelle 0.1 mg/d (9 months)
98USA10343	Seizure increased Taste alteration Drug interaction	Vivelle 0.075 mg/d (2 years)
96CDN12170	Seizure unclassified	Vivelle 0.075mg/d (less than 2 months)
98USA11206	Anaphylaxis	Vivelle 0.05mg/d (3 months)
*98CDN10271	Hypertension uncontrolled Uterine fibroids Uterine endometrial hyperplasia Pain leg Cramps abdominal Bloating Vision blurred Dyspnea Chest tightness Tenderness breasts Headache Application site reaction Dizziness	Vivelle 0.05mg/d (4 months)
97CDN10004	Palpitations Tenderness breasts Nausea Gallbladder spasms	Vivelle 0.05mg/d (3 weeks)
98CDN10001	Tachycardia	Vivelle 0.05 mg/d (6 months)
97CDN10382	Pain abdominal	Vivelle 0.0375 mg/d (2 days)

*Physician subsequently reported that this report is not an ADR as symptoms were present prior to initiation of Vivelle therapy.

Note: A review of the narrative for the first patient showed that the uterine neoplasm was a bleeding endometrial polyp (after 9-10 months of Vivelle 0.1 mg/day treatment); at this time, the patient also had breast abnormalities including enlargement of both breasts, increased density of both breasts and an architectural change in the left breast. A breast biopsy showed benign changes. The patient was scheduled for surgery for the polyp. No follow-up information is

available. Patient has also been taking micronized testosterone and progesterone (dose and regimen not given).

8.1.2.3.2 Published literature in support of efficacy and safety of Menorest

The sponsor presents a review of published reports of clinical studies with Vivelle and Menorest (estradiol transdermal system identical to Vivelle marketed by RPR outside the United States and Canada), as well as clinical studies of effects of progestogens on bone mineral density in postmenopausal women. The following is a brief summary of this review.

The sponsor identifies a total of 29 publications, including abstracts and review articles, that reported the results of clinical studies with Menorest. A bibliography is supplied in the NDA (Post-text supplement 4).

Two double-blind, placebo-controlled studies evaluated the efficacy of Menorest in prevention of postmenopausal osteoporosis. Women 1-6 years postmenopause, age 40-60 years, were randomized to receive Menorest (in doses of 0.025, 0.05 or 0.075 mg/day) or placebo continuously in one study (N=277) and Menorest 0.05, 0.075 or 0.1 mg/day or placebo sequentially for 25 days of each 28 day cycle in the other study (N=292). Both studies lasted two years and measured lumbar spine BMD as the primary efficacy endpoint. Patients in both studies received dydrogesterone (10 mg bid), a modification of progesterone, for 14 days per cycle.

Results: Treatment with all doses of Menorest resulted in a statistically significant increase in lumbar spine, femoral neck, trochanter, and total hip BMD after 2 years. Data for spinal BMD are shown in the following table:

Table 10.6-1 Mean percent change from baseline in BMD of lumbar spine (L1-L4) at 2 years

References	Menorest 0.025 mg/day	Menorest 0.05 mg/day	Menorest 0.075 mg/day	Menorest 0.1 mg/day	Placebo
14,15					
Mean %	2.9*	5.5*	6.9*	–	-1.8%
N	58	60	63		61
16,17					
Mean %	–	4.0*	5.4*	5.6*	-2.2
N		61	69	63	61

* $p \leq 0.0001$ compared to placebo

Bone turnover markers: Compared to placebo, after 2 years of treatment, the patients treated with Menorest had statistically significant (p-values $\leq$ 0.004) decreases in serum osteocalcin, serum bone-specific alkaline phosphatase and urinary type 1 collagen C-telopeptide/creatinine ratios.

Safety/tolerability:

Deaths: There was one sudden death in a patient reported to have cardiovascular risk factors, in a treatment group not specified in the paper.

Serious AEs: There were 14 patients with reported serious AEs in one study. These were distributed as follows: 4, 1 and 4 in the Menorest 0.025, 0.05 and 0.075 mg groups, respectively, and 5 in the placebo group. There were 12 patients with SAEs (2, 3 and 4 in the Menorest 0.05, 0.075 and 0.1 mg groups and 3 in the placebo groups) in the other study. This group included the one sudden death patient mentioned above. There was one case of jaundice and somnolence in a patient treated with Menorest 0.075 mg/day. This AE was thought to be possibly related to study medication. The other SAEs were not identified in the publications.

Frequent AEs: In these studies, the most frequently reported AEs were application site reactions, headache, rhinitis, abdominal pain, flu syndrome, back and breast pain.

In general, Menorest was well tolerated by the majority of patients in these studies.

8.1.2.3.3 120-day safety update

The database for the 120-day safety update consists of spontaneous safety/adverse event reports, plus an update of the review of published literature on Vivelle. The latest data encompass the period February 1999-Oct. 27, 1999. In addition, the sponsor has included similar updated worldwide safety data on Menorest, through the end of September 1999.

There are no new or ongoing trials with Vivelle.

The following is a brief review of this safety update.

The sponsor's table 2.1-1 (not reproduced here) lists all non-serious AE's submitted as spontaneous safety reports. The list is similar to AE's reported for postmenopausal patients taking HRT and for this population of postmenopausal women in general. Of interest, there were only 3 reports of vaginal bleeding. There were 18 reports of application site reactions, one report of blood pressure elevation, one report of abnormal LFTs, and 14 reports of lack of efficacy.

There were no deaths. There have been 8 serious AE's reported in the last 4 years. These have been summarized above in **table 15.2-1.**

Menorest-safety data: In the Menorest database, including results from 6 controlled clinical trials, the array of adverse events was very similar to the AE's that have been presented in this review of Vivelle. The 6 studies enrolled a total of 1213 patients, and 861 were treated with Menorest. In addition to collection and coding of all routine adverse events, some of the trials had additional safety studies related specifically to estrogenic effects on the reproductive system. As with the Vivelle trials, these included transvaginal ultrasound studies, uterine biopsies, mammograms, Pap smears, gynecological examinations, and vaginal bleeding assessments.

As with Vivelle, there was a tendency towards more reproductive system-associated AE's and weight gain in patients receiving the highest dose of Menorest. In a review of the submitted safety data, there were 37 serious adverse events in all studies and only 3 or 4 that were possibly or probably related to estrogen (one hypertension, one hyperlipidemia, one case of jaundice, and one breast neoplasm).

In the Menorest studies, there were two deaths and 3 cases of breast carcinoma. One patient, with a previous history of hypertension, had a fatal MI. The other patient also had a history of hypertension, as well as venous insufficiency, and hypercholesterolemia. One of the three instances of breast carcinoma occurred in a patient treated with placebo. The second presented with an advanced stage of breast carcinoma; she had been taking 0.1 mg of Menorest for 416 days. The third patient had breast cancer diagnosed 132 days after starting Menorest 0.075 mg.

Four other reports of death were in the CIOMS forms. These included: a death in a patient with a history of ASHD; one patient with recurrent ovarian cancer; one patient with ureteral cancer; and another patient who died following an intracerebral hemorrhage.

In summary the safety data on Menorest appear to be very similar to the experience with Vivelle. The overall safety data for both products are consistent with the larger experience with HRT in postmenopausal women.

9. Overview of Efficacy and Safety of Vivelle

9.1 Efficacy

Trial 035 was a 2-year study that randomized a total of 261 postmenopausal women at 20 centers in the United States. There was no randomization imbalance across the 5 treatment groups, in terms of baseline characteristics or demographics. Of the total randomized, 239 (92%) were included in the ITT population and 259 (99%) were included in the safety analysis.

However, it should be noted that the primary efficacy data (and much of the secondary efficacy data) were derived from only 180 patients. In this regard, it is worth commenting that the description of the evaluation plan and presentation of the data were confusing and internally inconsistent. According to the text in the clinical report, the efficacy data were supposed to have been derived from the ITT population; in fact, most of the data were taken from the subset of patients who completed the 104 weeks of the trial. Many of the tables and figures erroneously present data as derived from the entire ITT population. In a separate statistics review, the efficacy data were recalculated on the basis of the all-randomized population. These results were found to be consistent with those that were derived from the completer population. Thus the conclusions regarding efficacy are unchanged. However, efficacy claims should not be based on "all intent-to-treat patients," or on a patient number that is greater than the completer population (in fact, such claims are made in the proposed label).

These considerations do not apply to the safety analysis.

Protocol deviations occurred in 29% of patients, and were observed in all treatment groups. These were not considered likely to affect the analysis. I concur in this. Overall, the patient retention rates for this trial were roughly equivalent across treatment arms and adequate for evaluation of efficacy. The demographic and background characteristics of the population are typical of patients in osteoporosis trials, although this group was somewhat younger and heavier than usually encountered (see my earlier comments).

This study clearly met the primary efficacy goal, which was change from baseline AP lumbar spine BMD at 104 weeks. This was true for the completer and all-randomized populations. While the placebo patients lost an average of about 2% from baseline at 104 weeks (statistically significant), all 4 active treatment groups gained BMD at this skeletal site. The increases ranged from about 1.8% in the 0.025 mg group to nearly 6% in the highest dose (0.10 mg) group. The corresponding placebo-subtracted BMD differences ranged from about 3.5% in the lower doses to about 8.65% in the 0.10 mg group. In all 4 active treatment groups, the gains from baseline were statistically significant. In addition, all 4 doses of

Vivelle produced mean increases in spinal BMD that were statistically significantly different from the mean for the placebo group.

The mean increases in the 0.10 mg group were statistically significantly (and possibly clinically significantly) greater than those in the other 3 active treatment groups. However, the pairwise differences between effects of each of the 3 lower Vivelle doses were not statistically significant, despite a trend towards greater BMD increases in the 0.05 mg group, compared with the 2 lower dose groups.

In summary, it is clear that the lowest Vivelle dose, 0.025 mg, resulted in a statistically significant increase in lumbar spinal BMD over baseline and over placebo. However, the highest dose, 0.10 mg, produced BMD increases that were 2-3 times as great. There were no significant differences among the three lower doses, in terms of this (or any other) efficacy outcome.

Secondary endpoints: Similar results were found at the femoral neck and for whole body BMC, in that all doses of Vivelle produced significant increases over baseline. All doses of Vivelle were also significantly superior to placebo (all p-values $\leq$ 0.044) at Week 104, for both outcome variables. At these skeletal sites, the pairwise statistical comparisons between active treatment groups produced variable results. Vivelle 0.1 mg/day was superior to Vivelle 0.05 mg/day and 0.025 mg/day at the femoral neck. With respect to total body BMC, Vivelle 0.10 mg/day was superior to 0.025 mg/day (p=0.005), but not to the other 2 dose groups. Considerations related to the inconsistencies between ITT and completer populations also apply to all analyses of secondary endpoints.

With one exception (the 0.05 mg dose at Week 26), all doses of Vivelle were statistically superior to placebo at the AP lumbar spine and femoral neck at all measured time points throughout the trial. Thus, efficacy was achieved as early as 26 weeks.

For reasons that are inadequately explained by the sponsor, the DEXA results at the lateral lumbar spine were not entirely consistent with the above. All Vivelle doses produced results that were numerically superior to placebo. However, only Vivelle 0.1 mg/day was statistically superior to placebo at Week 104 (p=0.023). These results may have been due to greater variability in the BMD determinations at this skeletal site.

Co-administration of MPA (2.5 mg/day) had no apparent effect on % change from baseline in AP lumbar spine BMD at Week 104. However, as the number of MPA-treated patients was small (total 69 distributed over all 5 groups), the power was not sufficient to allow statistical differentiation of this possible effect of MPA. It should be noted that by now there are abundant data demonstrating that co-administration of MPA with estrogen does not interfere with the positive effects of the former on BMD.

The BMD results from study 035 are consistent with those reported for Menorest, a transdermal estradiol system that is identical to Vivelle. Two double-blind, placebo-controlled, 2-year studies involving 569 postmenopausal women showed % change from baseline in BMD of lumbar spine (L1-L4), femoral neck, trochanter and total hip were significantly greater in patients treated with Menorest 0.025, 0.05, 0.075 and 0.1 mg/day than patients treated with placebo ($p \leq 0.004$ for all comparisons with placebo).

Bone turnover markers: In this study, Vivelle failed to produce statistically significant reductions in serum osteocalcin or urinary NTX/creatinine, compared to placebo. This may have been due to marked intra- and inter-subject variability, as well as low numbers of patients in each treatment group. There was also no correlation between changes in bone markers and changes in BMD. In contrast, in the Menorest studies, the active drug statistically significantly reduced both markers of bone turnover, compared to placebo.

It should be noted that this study enrolled relatively young women who were within 5 years of menopause. Although patients were probably given sufficient supplemental calcium (1000 mg elemental calcium/day is sufficient if there is appreciable additional calcium in the diet), they were not properly supplemented with vitamin D. Thus the benefits of Vivelle, particularly the placebo-subtracted increases in BMD, may well have been greater than would have been observed in vitamin D-supplemented women and/or in women who initiated treatment later in life.

The BMD differences between the highest (0.10 mg) and lowest (0.025 mg) dose groups were about two- to threefold, depending on the skeletal site. These differences may be clinically important, in terms of translation into eventual fracture risk. Observational and case-controlled studies suggest that estrogen treatment after menopause is associated with decreased fracture risk. However, prospective, controlled clinical trials with fracture endpoints have not been conducted with estrogen replacement therapy. Consequently, a quantitative relationship between estrogen-induced BMD changes and possible decreases in fracture risk has not been established. Therefore, the clinical benefits of the relative or absolute BMD changes that are reported in this study are unknown. In particular, it is unclear whether a placebo-subtracted increase in spinal BMD of 8% is substantially superior to a 4% increase. Given the increase in adverse events associated with higher doses of estrogen, these considerations are important in deciding on estrogen replacement dose for osteoporosis prevention.

9.2 Safety

A total of 149 Vivelle treated patients were exposed to the drug for 1 year or longer. These were roughly equally distributed among the 5 treatment

arms. Overall, the adverse event profile that was observed in this study is consistent with the known effects of estrogen/progestin. In addition, Vivelle appeared to be well tolerated.

The most frequently reported AEs were breast pain and vaginal bleeding. As expected, these occurred in the active treatment groups and were more frequent in the highest dose group (Vivelle 0.1 mg/day). The majority of all AEs were mild to moderate in severity.

There were no deaths.

Nonfatal SAEs were reported in 9 Vivelle treated patients and 4 placebo patients. Only one, a DVT in a Vivelle 0.025 mg/day patient, was considered trial drug-related by the investigator. An examination of the other 12 shows no pattern of serious AE's occurring predominantly in the Vivelle-treated patients. There was a small increase in occurrence of "reproductive system neoplasms," in the 0.10 mg group, but these were benign.

AEs leading to discontinuation occurred more frequently in Vivelle-treated groups (9% to 25%), than the placebo group (3%). Discontinuation for adverse events occurred more frequently in the highest dose group. The most frequent AE leading to discontinuation was vaginal bleeding. This occurred in 11 patients, 7 in the 0.10 mg group, four in the other active treatment groups, and none in placebo. Two patients discontinued due to DVT: one in the 0.10 mg group and one in the 0.025 mg group.

Application site reaction was reported in 6% to 11% of patients in active treatment groups and 10% of placebo patients.

Endometrial evaluations at the final visit in 73 nonhysterectomized patients showed no evidence of hyperplasia, indicating efficacy of concomitant treatment with MPA. However, vaginal bleeding occurred significantly more frequently in the Vivelle 0.1mg group. In study 036, routine transvaginal ultrasound disclosed increased endometrial thickness in Vivelle-treated patients (0.0375 mg), compared to placebo. Biopsy disclosed simple hyperplasia in 2 patients.

Mammographic examination disclosed three patients in the 0.10 mg group with abnormalities (small cyst, altered parenchymal pattern, and fibrocystic changes) thought to be drug-related. Two patients in the 0.0375 mg group had changes at Week 52 that disappeared on subsequent examinations.

There were no clinically significant abnormalities in other laboratory safety studies that were clearly drug-related.

Review of the 120 day safety report and a summary of all serious AEs received as spontaneous reports since the drug was marketed show no unanticipated adverse events. A review of the safety data for Menorest leads to the same conclusion.

10. Conclusions

This study showed that Vivelle, in doses of 0.025 mg to 0.1 mg per day delivered as a transdermal patch, is effective in preventing bone loss (spine, femoral neck, and total body) in a population of postmenopausal women who were studied within 5 years of natural or surgical menopause.

The minimum effective dose of Vivelle was 0.025 mg/day. However, Vivelle, 0.1 mg per day, was shown to be consistently superior in efficacy to the three lower doses in increasing BMD.

It is possible that the placebo-subtracted efficacy of Vivelle would have been less than observed if the patients had been supplemented adequately with vitamin D. Additionally, the bone-sparing effects of Vivelle may be less pronounced in women who initiate treatment later in life.

The safety/tolerability profile for Vivelle was consistent with prior experience with estrogen replacement regimens. The safety profiles of Vivelle and Menorest are essentially the same. It should be emphasized that the highest dose of transdermal estradiol, 0.10 mg/day, was associated with significantly greater numbers of estrogen-related adverse events than were found with the lower doses. Most of the adverse experiences that were found in this trial were fairly benign and reversible (e.g., bleeding, breast tenderness). On the other hand, the trial population was too small, and the time frame too short, to capture more serious and long term potential side effects of estrogen (e.g., promotion of breast cancer). The concern is not whether there are unknown side effects associated with Vivelle, because we have by now vast experience with estrogen replacement regimens. Rather, the issue is whether the risks of the highest dose of Vivelle are worth the benefits for an osteoporosis prevention indication by itself. These considerations are important in choosing a dose of Vivelle for a given patient. If the dose is chosen on the basis of treatment of postmenopausal symptoms, then the endpoints are clear and doses can be adjusted accordingly. On the other hand, if the major, or only, goal of therapy in a particular patient is prevention of bone loss, then the choice of dose may be problematic because the endpoints are not immediate. Therefore, the label should provide safety and efficacy data that are sufficient to permit selection of a dose that best meets the therapeutic goals of individual patients.

10.1 Significant/potentially significant events: none.

10.1.1 Deaths: none.

10.1.2 Other Significant/Potentially Significant Events: none in this trial.

10.1.3 Overdose experience: none reported in this trial.

10.2 Other Safety Findings: none.

10.2.2 Laboratory Findings: no significant new findings were reported.

10.2.3 Special Studies: see above under uterine safety, vaginal bleeding assessment, and mammography.

10.2.4 Drug-Demographic Interactions: not studied in this sNDA.

10.2.5 Drug-Disease Interactions: none reported or specifically studied in this sNDA; precautions regarding pre-existing diseases and other conditions are included in current estrogen labels.

10.2.6 Drug-Drug and Drug-Laboratory Interactions: with the exception of observations regarding the co-administration of MPA, these were not studied in this sNDA; known drug-laboratory interactions are currently included in estrogen labels.

10.2.7 Withdrawal Phenomena/Abuse Potential: none reported or known.

10.2.8 Human Reproduction Data: Estrogens are contraindicated in pregnancy (Pregnancy Category X). This is indicated in a black box warning in the current label. Precautions for nursing mothers are included in current estrogen labels.

10.2.9 Pediatric use: as indicated in the label, the safety and efficacy of this product in pediatric patients have not been established. Pediatric studies have not been requested.

11 Labeling Review: Electronic and paper copies of the proposed labeling changes have been submitted. Unfortunately, the electronic submission could not be reproduced adequately and will be appended to this review, with recommended changes.

12. Recommendations:

Approval, with modifications in the label. This approval is based on demonstrated efficacy and safety. Efficacy has been demonstrated based on analyses of completers and of all-randomized patients. However, any quantitative claims regarding the degree of efficacy must be based on ITT data. I recommend that any numerical data that are included in the label or in advertising claims represent true ITT data. The sponsor should recalculate data to fit a true ITT analysis. This applies also to the proposed figure (see label). Data that are derived from a completers analysis

obviously cannot be labeled as derived from an ITT population. In addition, I recommend that completers-derived data not be used (even if labeled appropriately) because that approach differs from recommendations in our guidelines. Additionally, this would not provide uniform regulatory policy.

/S/ /S/

BRUCE S. SCHNEIDER, MD

Medical Officer, DMEDP, ODE II, HFD-510

Cc Drs Jenkins, Rarick, Colman, Stadel, Zilberstein, Mr. Koch HFD-510 file