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APPLICATION NUMBER:
203752Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number 203752
Priority or Standard Standard

Submit Date December 29, 2012
Received Date December 29, 2012
PDUFA Goal Date October 29, 2012
Division/Office Division of Reproductive and
Urologic Products
(DRUP)/Office of Drug
Evaluation III (ODE III)

Reviewer Name Phill H. Price, M.D.
Review Completion Date September 24, 2012

Established Name Estradiol transdermal system
(Proposed) Trade Name Minivelle
Therapeutic Class Estrogen
Applicant Noven Pharmaceuticals, Inc.

Formulation Transdermal Patch
Dosing Regimen 0.0375 mg per day twice
weekly initially allowing for
titration upward (0.05 mg,
0.075 mg, and 0.1 mg of
estradiol per day if necessary
depending upon relief of

	symptoms
Indication	Treatment of Moderate to Severe Vasomotor symptoms due to menopause
Intended Population(s)	Healthy Postmenopausal Women

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

Approval of NDA 202752 is recommended. The sponsor has demonstrated bioequivalence to Vivelle (transdermal delivery system). Since its approval in 1994 Vivelle has been shown to be safe and efficacious.

1.1 Recommendation on Regulatory Action

Approval of NDA 202752 is recommended.

1.2 Risk Benefit Assessment

Since the initial approval of Vivelle[®] in 1994 and Vivelle-Dot[®] in 1996 these products have had a positive risk-benefit ratio. NDA 202752 is the same product as Vivelle and Vivelle-Dot, but is designed to deliver the same amounts of estradiol in a smaller transdermal delivery system with similar risk and benefits based upon the pivotal bioequivalence Study N28004.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no need for a Risk Evaluation and Mitigation strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

No additional postmarketing action is recommended.

2 Introduction and Regulatory Background

Vivelle (NDA 20-323) was initially approved October 28, 1994. Vivelle has not been commercially available since 2006. The doses initially sought for approval were 0.0375mg, 0.05 mg, 0.075mg, and 0.1mg of estradiol per day. In the initial review cycle the 0.075mg and 0.1mg per day doses were shown to demonstrate efficacy at weeks 4 through week 12. The 0.050mg/day dosage did not demonstrate efficacy at weeks 4 through 12. The efficacy of the 0.050mg/day dose was accepted based on bioequivalence to another estradiol transdermal system. The Vivelle 0.0375mg/day did not demonstrate efficacy until the sixth week of treatment. Therefore, the 0.0375mg/day dose was approved in October 1994 with restrictive language stating that "*women taking the 0.035mg/day dosage may experience a delay in the onset of efficacy.*" The sponsor agreed to a Phase 4 study that would define the percentage of patients who received relief of vasomotor symptoms at the lowest dose (0.0375 mg/day). A phase 4 study was conducted under Supplement 021. Supplement 021 addressed the sponsor's original Phase 4 commitment dated March 24, 1994. The study presented in

Supplement 021 was a randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of the 0.0375mg/day dose of Vivelle; approximately 259 subjects were enrolled. The sample size was sufficient to detect a mean difference of 2.0 per day in the reduction of total number of hot flashes for Vivelle vs. placebo. In cycle 1 the mean difference was -3.0 (ITT) and this was maintained through cycles 2 and 3 (-3.21, -3.59, p-value <0.001). Severity was also statistically significant different in cycles 2 and 3. This supplement provided evidence that the lowest dose of Vivelle 0.0375 mg per day was statistically significant different from placebo at the end of weeks 4, 8 and 12 in the treatment of moderate to severe vasomotor symptoms.

Vivelle-Dot (NDA 20-538) was approved on July 31, 1996 after demonstrating bioequivalence to Vivelle. The same restrictive language for the 0.0375mg/day dose applied to Vivelle-Dot. This restrictive language was removed after completion of the Phase 4 commitment (Supplement 021) on February 25, 2000. Supplement 021 demonstrated that Vivelle 0.0375 was statistically significant different from placebo at the end of weeks 4, 8 and 12. In addition, under S015 Vivelle-Dot was approved for the prevention of osteoporosis in 2002.

2.1 Product Information

Noven Pharmaceuticals, Inc is developing Minivelle, a smaller estradiol transdermal system (ETS) compared to the marketed Vivelle-Dot (approximately 60% of the size of Vivelle-Dot. Minivelle has the same multipolymeric adhesive platform as Vivelle-Dot and it releases 17β -estradiol continuously upon application to intact skin, and has a target absorption profile similar to that of Vivelle-Dot. Vivelle-Dot is manufactured by Noven and marketed by Novartis Pharmaceutical Corporation in five different estradiol strengths (0.025 mg/day to 0.1 mg/day) with corresponding active surface areas (2.5 cm² to 10 cm²). Minivelle is available in (b) (4) dosage strengths that have been designed to deliver the same therapeutic levels of estradiol as Vivelle and Vivelle-Dot, but with a smaller active surface area. (b) (4)

17β -estradiol is the primary estrogenic hormone secreted by the human ovary. Loss of ovarian estradiol secretion at the onset of menopause or after bilateral oophorectomy is associated with vasomotor symptoms (hot flashes and night sweats). Hot flashes are recurrent, transient episodes of flushing, perspiration, and a sensation ranging from warmth to intense heat on the upper body and face, sometimes followed by chills. Hot flashes that occur with perspiration during sleep are termed night sweats. Systemic hormone therapy (HT) is considered to be the therapeutic standard for the treatment of hot flashes. Treatment of moderate to severe menopause symptoms (including hot flashes) is the primary indication for systemic hormone therapy.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Estrogen-Alone Products	Available Dosage Strengths
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Cenestin® (synthetic conjugated estrogens, A)	0.625 mg, 0.9 mg, or 1.25 mg once daily
Enjuvia® (synthetic conjugated estrogens, B)	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Menest® (esterified estrogens)*	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Estrace® (estradiol)	0.5 mg, 1.0 mg, or 2.0 mg once daily
Femtrace® (estradiol acetate)	0.45 mg, 0.9 mg, or 1.8 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Transdermal Products	Available Dosage Strengths
Alora® (estradiol matrix patch)	0.025 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Climara® (estradiol matrix patch)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied once weekly
Esclim® (estradiol matrix patch)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Menostar® (estradiol matrix patch)	0.014 mg/day; patch applied once weekly
Vivelle® (estradiol matrix patch)	0.05 mg/day or 0.1 mg/day; patch applied twice weekly
Vivelle Dot® (estradiol matrix patch)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Various Generics (estradiol matrix patch)	0.05 mg/day or 0.1 mg/day; patch applied once or twice weekly
Estraderm® (estradiol reservoir patch)	0.05 mg/day or 0.1 mg/day; patch applied twice weekly
Topical Products	Available Dosage Strengths
EstroGel® 0.06% (estradiol gel)	0.075 mg/day; 1.25 gram gel applied once daily
Elestrin® (estradiol gel)	0.52 mg/day or 1.04 mg/day; 0.87 gram or 1.7 gram applied once daily
Divigel (estradiol gel) 0.1%	0.25 mg/day, 0.5 mg/day, or 1.0 mg/day; 0.25 gram, 0.5 gram or 1.0 gram applied once daily
Estrasorb® (estradiol topical emulsion)	0.05 mg/day; two 1.74 gram pouch applied once daily
Evamist® (estradiol transdermal spray)	1, 2 or 3 spray(s) 90 mL containing 1.53 mg estradiol applied once daily
Vaginal Cream	Available Dosage Strengths
Premarin® (conjugated estrogens) Vaginal Cream	0.5 to 2 grams (0.625 mg per gram) inserted intravaginal daily
Estrace (estradiol) Vaginal Cream	2 to 4 grams (0.1 mg per gram) inserted intravaginal daily for 1 to 2 weeks, then 1 gram inserted intravaginal daily thereafter
Vaginal Rings	Available Dosage Strengths

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 Minivelle (estradiol transdermal delivery system)

Estring® (estradiol)	Release of 7.5 mcg estradiol/day; ring is worn for 90 days
Femring® (estradiol acetate)	Release of 0.05 mg estradiol/day or 0.10 mg estradiol/day; ring is worn for 90 days
Vaginal Tablet	Available Dosage Strengths
Vagifem® (estradiol hemihydrate)	10 mcg/day or 25 mcg/day; vaginal tablet is inserted twice weekly

Table 1: Estrogen-Plus Progestin Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Estrogen Plus Progestin Products	Available Dosage Strengths
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE/day plus 1.5 mg MPA/day taken daily or 0.625 mg CE/day plus 2.5 mg or 5.0 mg MPA/day taken daily
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE/day taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA/day taken daily on days 15-18
femhrt® (ethinyl estradiol [EE] plus norethindrone acetate [NETA])	2.5 mcg EE/day plus 0.5 mg NETA/day taken daily or 5 mcg EE/day plus 1.0 mg NETA/day taken daily
Activella® (estradiol [E2] plus norethindrone acetate [NETA])	0.5 mg E ₂ /day plus 0.1 mg NETA/day taken daily or 1 mg E ₂ /day plus 0.5 mg NETA/day taken daily
Angeliq® (estradiol [E2] plus drospirenone)	1 mg E ₂ /day plus 0.5 mg drospirenone/day taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E ₂ /day taken daily for 3 days, then 1 mg E ₂ plus 0.09 mg norgestimate/day taken daily for 3 days, repeated continuously
Transdermal Estrogen Plus Progestin Products	Available Dosage Strengths
CombiPatch (estradiol [E2] plus norethindrone Acetate [NETA])	0.05 mg E ₂ /day plus 0.14 mg NETA/day; patch applied twice weekly 0.05 mg E ₂ /day plus 0.25 mg NETA/day; patch applied twice weekly
ClimaraPro® (estradiol [E2] plus levonorgestrel)	0.05 mg E ₂ /day plus 0.015 mg levonorgestrel/day; patch applied once weekly

Table 1: Progestin Products Used in Combination with Conjugated Estrogens Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Progestogen Tablet or Capsule	Available Dosage Strengths
Provera® (medroxyprogesterone acetate [MPA])	2.5 mg/day, 5 mg/day or 10 mg/day taken once daily for 12 days of each 28-day cycle
Various Generics	2.5 mg/day, 5 mg/day or 10 mg/day taken once daily for 12 days of each 28 day cycle
Prometrium® (progesterone in peanut oil)	100 mg/day or 200 mg/day taken daily for 12 to 14 days of each 28-day cycle

2.3 Availability of Proposed Active Ingredient in the United States

Minivelle contains estradiol in a multipolymeric adhesive. The system is designed to release 17β -estradiol, the active pharmaceutical product (API), continuously upon application to intact skin. Estradiol USP (17β -estradiol) is a white, crystalline powder, chemically described as estra- 1, 3, 5 (10)-triene-3, 17β -diol. The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.38.

Minivelle is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a flexible backing film; 2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol (OA), Povidone-^{(b) (4)} and dipropylene glycol (DPG); and 3) a polyester release liner that is attached to the adhesive surface and must be removed before the patch can be used.

In addition to the API 17β -estradiol (E_2), the drug-in-adhesive matrix contains ^{(b) (4)} excipients: ^{(b) (4)}

Based upon previous experience, ^{(b) (4)} The 16 formulations were studied in a multivariate factorial (4 by 4) skin permeability study (coat weight, ^{(b) (4)} Five formulations were selected and further assessed in skin permeability studies versus Vivelles-Dot and Vivelles in multiple skin donors. The three formulations with the highest average flux, when compared to Vivelles-Dot and Vivelles, were selected for further study.

2.4 Important Safety Issues With Consideration to Related Drugs

Large prospective studies such as the Heart and Estrogen-Progestin Replacement Study and the Women's Health Initiative have assessed the risks associated with the use of hormone replacement therapy (HRT). Following the publication of the long-term effects of hormone therapy (HT) in these large randomized controlled trials specifically regarding the increased risk of breast cancer, coronary heart disease, and venous thromboembolism, questions remain regarding of long term benefit/risk profile with the use of estrogen products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting was held between DRUP and the sponsor on September 11, 2007 to discuss the developmental plan for Minivelle. Key recommendations by the Division to the sponsor are as follows:

- No preclinical studies were necessary if the patch and matrix and the impurities and degradation products of Minivelle were qualitatively and quantitatively similar to Vivelle and Vivelle-Dot
- A pivotal, single dose, two-way crossover, bioequivalence study comparing the highest strength of Vivelle to the highest strength of Minivelle would provide support for approval of Minivelle. The Division stated the following with regards to the bioequivalence study:
 - Vivelle should be used as the reference in the study since the clinical trials were conducted with Vivelle and Vivelle 0.1 and 0.05 mg/day ETS were still commercially available at the time of the pre-IND meeting
 - The bioequivalence requirement for lower strengths of Minivelle would be waived based on information of dose proportionality, proportionally similar composition, and a comparison of the in-vitro dissolution profiles of Minivelle and Vivelle
 - Bioequivalence should be based on both baseline corrected and uncorrected relevant pharmacokinetic parameters
- A single-dose, crossover study with at least three strengths of Minivelle should be conducted to determine the dose proportionality of Minivelle
- The dermal characteristics (i.e., adhesive properties, skin irritation, and discomfort) of Minivelle should be evaluated in the bioequivalence dose/proportionality studies.

On March 18, 2011 the Division sent Noven a written response on the design of the dose proportionality study and reiterated the need for a dose proportionality study. The Division agreed that measurement of estradiol and estrone would be sufficient. In addition a full 24-hour baseline measurement of estradiol and estrone concentration and a standardized adhesion scale should be used to assess adhesion of Minivelle. Both recommendations were incorporated into the final protocol.

2.6 Other Relevant Background Information

All relevant background information as conveyed in the preceding sections.

3 Ethics and Good Clinical Practices.

3.1 Submission Quality and Integrity

At the request of DRUP and the Division of Clinical Pharmacology III, the Division of Bioequivalence and GLP Compliance (DBGC) conducted audits of the clinical and analytical portion of the bioequivalence Study N28-004. The audits were conducted at Elite Research Institute, Inc., Miami and at (b) (4) during the period of (b) (4). The audits included a thorough examination of study record, facilities, and equipment, and interviews and discussions

with the firms' management and staff. Following the inspections at the clinical and analytical sites, *no significant* objectionable conditions were observed and Form 483 was not issued.

3.2 Compliance with Good Clinical Practices

This study was conducted in compliance with Good Clinical Practices (GCPs) and ICH Guidelines of GCP and was conducted in full compliance with the principles of the World Medical Assembly Declaration of Helsinki and its most recent amendments. This study received IRB approval prior to commencement. Written informed consent for the study was obtained from all subjects before any study-related procedures were performed.

3.3 Financial Disclosures

Form FD 3454, dated December 23, 2011 was signed by Sean Russell, the Associate Director, Regulatory Affairs for Noven. Per the applicant, each listed clinical investigator disclosed no "proprietary interest in this product or a significant equity in the sponsor" as defined in 21 CFR 542(b).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Since the approval of Vivelle and Vivelle-Dot a Black Box Warning has been required for all estrogen and estrogen/progestin drug products. Updated information in this Black Box Warning relates to information obtained in the Women's Health Initiative (WHI) and the Women's Health Initiative Memory Study (WHIMS). In addition, the Black Box Warning retains information regarding the increased risk of endometrial cancer.

4.1 Chemistry Manufacturing and Controls

The Chemistry and Manufacturing reviews recommended approval of this NDA. During the review cycle several clarifications were required to qualify a more distinguishable ink to Minivelle. The sponsor will launch their commercial product utilizing (b) (4) ink and continue to utilize (b) (4) ink while completing their qualification and stability work of a more distinguishable ink for Minivelle.

4.2 Clinical Microbiology

Microbiology was not consulted for this application.

4.3 Preclinical Pharmacology/Toxicology

There are no preclinical/toxicology issues related to this NDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women. The pharmacologic effects of ethinyl estradiol are similar to those of endogenous estrogens.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

4.4.2 Pharmacodynamics

There were no Pharmacodynamic studies conducted with this submission.

4.4.3 Pharmacokinetics

The primary study to support the bioequivalence of (b) (4) (Minivelle) to Vivelle 0.1mg was study protocol N28-004. Subjects were enrolled from February 2, 2011 (first subject enrolled) to May 5, 2011 (last subject enrolled). This was a Phase 1, open-label, single-center, randomized, single-dose, two-way crossover study in 100 healthy, non-smoking postmenopausal women (aged 40 to 65 years, inclusive). Subjects were

housed during each treatment period from approximately 36 hours prior to dosing through the 120-hour post-dose assessment.

Each subject received a single dose of each of the two treatments. Each transdermal system was worn for 84 hours. There was a minimum washout period of at least 14 days between the 120-hour assessments of treatment one and the administration of the second treatment. Eligible subjects reported to the clinic on Day -1 and Day 21 in the evening at approximately 1900 hours and subjects were housed during each treatment period.

The two treatments included in this study were:

- **Treatment A** (test): one (b) (4) ETS patch (1.65 mg/6.6 cm²) applied for 84 hours. The application was applied to the abdomen below the umbilicus to a clean dry, no-oily, non-irritated area.
- **Treatment B** (reference): one Vivelle ETS patch (8.66 mg /29.0 cm²) applied for 84 hours. The application was applied to the abdomen below the umbilicus to a clean dry, no-oily, non-irritated area.

See Sponsor's Table 9-1 –Schedule of Activities and Assessments. This table is numbered 24 in the Appendix

The trial consisted of:

- A screening period (maximum duration of 21 days), and
- The confinement/treatment and washout periods (29 days in duration).

Screening Period

Healthy, postmenopausal women meeting all the eligibility criteria were selected for the study within three weeks of the first treatment administration. The following procedures were performed at the screening visit:

1. A signed consent was obtained. No screening procedures could be initiated prior to the subject signing the informed consent form.
2. A screening number was assigned. Subjects were assigned screening numbers sequentially.
3. A complete medical history was obtained and included significant acute/chronic medical illnesses, and past major surgical procedures.

4. Demographic information, including age, gender, ethnicity, race, was recorded.
5. Complete physical and gynecological examinations including breast and pelvic examination were performed. A Pap smear was performed unless one had been conducted within three months of the screening visit and results could be provided. A mammogram was also obtained unless one had been conducted within nine months of screening visit and results could be provided. A transvaginal ultrasound was performed on subjects with an intact uterus to determine normal endometrial lining and thickness. All abnormal findings were recorded in Medical History.
6. Vital signs, including sitting BP, HR, and oral body temperature, were obtained.
7. Blood and urine was collected for the following laboratory assessments:
 - Hematology
 - Blood Chemistry
 - Urinalysis
 - Urine Drug Screen
 - Serum screen for Hepatitis B surface antigen, Hepatitis C antibody, and HIV antibody
 - Hormone Levels:
 - Estradiol
 - Follicle Stimulating Hormone (FSH) If the initial screening FSH level was below 40 mIU/mL and the test was repeated a second time, then the average of the first and second samples was used to make the final determination for eligibility.
 - Luteinizing Hormone (LH).
8. A 12-lead electrocardiogram (ECG) was performed.
9. A breathalyzer test was conducted to determine alcohol use.
10. All medications taken within 30 days prior to screening were recorded.

The Investigator reviewed all screening assessments and documented the eligibility of each subject.

Study Population

Inclusion Criteria

Inclusion Criteria included:

1. Subjects who were willing and able to be compliant with the protocol and provide voluntary written informed consent

2. Subjects who were healthy postmenopausal, non-smoking women of any race between the ages 40 and 65 years, at screening (inclusive).
Postmenopausal status was defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL, or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
3. Documentation of bilateral oophorectomy surgery was required for review.
4. The subject had body mass index (BMI) of 18.5 to 29.9 kg/m², inclusive.
5. Subjects who were judged by the Investigator and the Sponsor to be healthy on the basis of pre-study medical history, physical examination, electrocardiogram, and clinical laboratory test results.
6. Subjects who had documentation of a negative screening mammogram (obtained at screening or within nine months of study enrollment) and normal clinical breast examination prior to enrollment in study.
7. Any subject with an intact uterus should have baseline vaginal ultrasonography demonstrating inactive endometrial lining with endometrial thickness less than 5mm.
8. Subjects who had screening serum estradiol levels ≤ 20 pg/mL.
9. Subjects who had serum follicular stimulating hormone levels (FSH) ≥ 40 mIU/mL.

Reviewer's comment

Inclusion Criteria are acceptable for this pharmacokinetic study. However, a BMI up to 38 kg/m² would have been more reflective of the U.S. population of women.

Exclusion Criteria

1. Male subjects.
2. Premenopausal, perimenopausal, pregnant or lactating subjects.

3. Findings that indicated any suspicion of breast malignancy.
4. Any subject with tobacco use, obesity, undiagnosed abnormal genital bleeding or a history of significant risk factors for endometrial cancer
5. Any subjects with a history of venous thromboembolism, pulmonary embolism, stroke, endometrial cancer, breast cancer, cholestatic jaundice, hypertension, serious heart problems, heart failure, myocardial infarction, ventricular arrhythmia, exertional chest pain, insulin dependent diabetes, hypercholesterolemia, hypertriglyceridemia, systemic lupus erythematosus, impaired liver function, or significant renal dysfunction.
6. A medical history of condition that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as human immunodeficiency virus (HIV) positive or AIDS, allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, rheumatoid arthritis or systemic lupus erythematosus).
7. A medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
8. A history of significant dermatologic cancers (e.g., melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the application sites.
9. Any subject with a recent history or presence of glaucoma, migraines, cardiovascular, hepatic, renal, gastrointestinal, neurologic, psychiatric, dermatologic, pulmonary, cerebrovascular, endocrine, hematologic, thromboembolic, immunologic disease or any other disorder which requires physician care.
10. Subjects who had existing medical conditions which might interfere with absorption, distribution, metabolism, or excretion of study medication.
11. Any subjects with a history of breast cancer, clinically significant fibrocystic breast disease, breast nodules, or uterine cancer.
12. Baseline blood pressure (BP) < 90/50 or > 150/90 mmHg.
13. Sitting heart rate (HR) < 45 or > 90 beats/min.
14. Any clinically significant ECG finding or QTcF interval > 470 msec.

15. Evidence of orthostatic hypotension (decrease of $> 20/10$ mmHg at 2 min after assuming upright posture after 5 min of sitting) accompanied by symptoms (faintness, lightheadedness, dizziness, confusion).
16. Hemoglobin < 12 g/dL and hematocrit $< 40\%$.
17. Clinical laboratory test results outside of the normal range for the laboratory conducting the test (unless approved by the Sponsor).
18. Any subject who had received a positive urine pregnancy test result at screening or any time during study participation.
19. Any subject with a history of sensitivity to estrogen or related derivatives.
20. Any subjects with a history of significant allergies (including food, asthma, or drug allergies).
21. Any subject with a history of allergy to soaps, lotions, cosmetics, or adhesives.
22. Any subjects with an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application sites, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
23. Presence of open sores at the application sites.
24. Any subjects with a history of significant skin disorder.
25. Any subjects with a present or past history of narcotic addiction, drug abuse, or alcoholism.
26. Any subjects who had smoked or used tobacco during the last 6 months prior to screening
27. Any subject who had donated one or more pints of blood within 30 days prior to treatment administration.
28. Any subject who had symptoms of any significant acute illnesses at the screening visit.
29. Any subjects who had used any of the following hormone replacement therapies within the specified time prior to the screening visit:
 - a. vaginal hormonal products for at least one week (rings, creams, gels)

- b. transdermal estrogen alone or estrogen/progestin containing products for at least 4 weeks
 - c. oral estrogen and/or intrauterine progestin therapy for at least 8 weeks
 - d. progestin implants and estrogen alone injectable drug therapy for at least 3 months
 - e. estrogen pellet therapy or progestin injectable drug therapy for at least 6 months
 - f. percutaneous estrogen lotions/gels for at least 4 weeks.
30. The use of medications or treatments within 3 weeks prior to dosing that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
31. Any subject who had used any investigational drug within 30 days prior to treatment administration.
32. Any subject who had used any prescription medications within 14 days of the screening visit.
33. Subjects who had used any over the counter preparations including herbal or nutritional supplements and multivitamins within 10 days prior to screening.
34. Subjects who consumed foods or beverages containing caffeine/xanthine, or alcohol within 72 hours prior to receiving the first study treatment.
35. Any subject who had received a positive screen for hepatitis B surface antigen (HBsAg) or hepatitis C antibody.
36. Any subject who had received a positive screen for the Human Immunodeficiency Virus (HIV) antibody.
37. Any subject who had received a positive urine drug screen.
38. Any subject who had any clinically significant illness within 90 days prior to receiving the first dose of study medication.

Reviewer's comment

The exclusion criteria are very extensive and would be too exclusionary for a clinical trial containing efficacy data for evaluation. No new efficacy data was obtained in this trial. The exclusion criteria are acceptable for this pharmacokinetic study.

Pharmacokinetic Assessments

Blood samples were collected at times specified by the protocol and the obtained serum samples were analyzed for estradiol, unconjugated estrone, and total estrone concentrations. The liquid chromatography tandem mass spectrometry (LC/MS/MS) method was adequately validated with minimum quantifiable levels of detection (LLOQ) being 1.0, 5.0, and 10 pg/mL for estradiol, unconjugated estrone, and total estrone, respectively.

Pharmacokinetic (PK) parameters were calculated from the obtained serum concentrations for each subject included in the PK population.

The following PK parameters were calculated for baseline uncorrected estradiol, baseline corrected estradiol, unconjugated estrone, and total estrone:

- C_{max} : the maximum serum concentration observed
- AUC_{84} : the area under the serum concentration-time profile; calculated from time 0 to 84 hour (wear time)
- AUC_{last} : the area under the serum concentration-time profile; calculated from time 0 to the last measurable concentration by the linear trapezoidal rule
- AUC_{inf} : the area under the serum concentration-time profile extrapolated to infinity
- T_{max} : the time of the maximum observed concentration
- k_{el} : elimination rate constant (slope of the log concentration vs. time curve between 84 and 120 hours)
- $t_{1/2}$: elimination half-life ($\ln 2/k_{el}$)

The statistical analysis of the bioequivalence (BE) data included the construction of 90% confidence intervals (CIs) for Test/Reference ratios for baseline un-corrected estradiol C_{max} , AUC_{84} , and AUC_{last} and for baseline-corrected estradiol C_{max} , AUC_{84} , AUC_{last} , and AUC_{inf} and was performed in accordance with the US Food and Drug Administration's *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence* (January 2001)

AUC_{84} , AUC_{last} , and AUC_{inf} are the most important pharmacokinetic parameters in this review since this is a 3-4 day transdermal patch and consistent serum levels of E_2 are

essential for control of vasomotor symptoms from initiation of patch wear to patch change. Importantly, in the initial study review in 1994 neither the 0.0375mg/day nor the 0.05 mg/day patch demonstrated effectiveness until the 6th treatment week.

Dermal Evaluations

Site personnel evaluated the application site for adhesion of the system to the skin and for any irritation or discomfort caused by it. Spontaneous complaints of dermal reactions at unscheduled times were also recorded in dermal evaluation forms. Spontaneous reports could include the following: initial dermal response or discomfort, exacerbation of an existing response or discomfort. The time elapsed between the unscheduled evaluation and ETS application was recorded.

System Adhesion

During the period of ETS wear, the adhesion of the transdermal systems was evaluated at 2, 4, 8, and 12 hours and then every 12 hours until ETS removal. All evaluations were completed within \pm 10 minutes of the scheduled time. Findings were recorded as an estimate of the percentage of the system surface in contact with the skin, according to the scale in the following table;

Sponsor's Table 9-3

Table 2: System Adhesion Scale

Score Definitions	
0	\geq 90% adhered (essentially no lift off the skin)
1	\geq 75% < 90% adhered (some edges only lifting off the skin)
2	\geq 50% < 75% adhered (less than ½ of the system lifting off the skin)
3	< 50% adhered but not detached (more ½ the system lifting off the skin without falling off)
4	System detached (patch completely off the skin)

Sponsor Table 9-4

Table 3: Dermal Reactions

Dermal Response	Grade
No erythema (redness)	0
Very slight erythema, barely perceptible	1
Definite erythema, readily visible; minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the test site	7

Other effects such as a glazed appearance, cracking fissures and exudates were given letter ratings where applicable. In addition the subject was asked to describe her discomfort and this was given a numerical score.

Immediately following the removal of the transdermal system at 84 hours the amount of adhesive residue remaining at the application site was examined and graded to a scale of 0-4. The scores were as follows: 0 no residue, 1 light residue, 2 medium residue, 3 heavy residue and 4 patch detached (completely off the skin).

Dermal Evaluation

All dermal evaluations (i.e. Adhesion, Discomfort, Skin irritation and Adhesive residue) were listed and summarized.

Safety Analyses

Adverse Events (AEs) were classified by system organ class (SOC) and preferred term (PT) using MedDRA (version 12.1).

All AEs that occurred after the first dose of randomized study treatment were summarized, using frequency counts and percentages, by treatment group. Adverse events with start dates prior to the first dose date were listed as pre-dose events. All other Adverse Events (AEs) were classified by system organ class (SOC) and preferred term (PT) using MedDRA (version 12.1). All AEs that occurred after the first dose of randomized study treatment were summarized, using frequency counts and percentages, by treatment group. Adverse events with start dates prior to the first dose date were listed as pre-dose events. All other AEs were considered treatment-emergent adverse events (TEAE) based on the onset date and time of the event respective to the dosing date and time for the treatment period.

The incidence of TEAEs for each treatment were summarized as follows:

- Number (%) of subjects having one or more TEAE for all AEs, and for each MedDRA preferred term.
- Number (%) of subjects having one or more TEAE by each severity grade and MedDRA preferred term.
- Number (%) of subjects having one or more TEAE by each relationship category and MedDRA preferred term.
- Serious Adverse Events (SAEs) were to be listed by preferred term, summarized by treatment and preferred term if the number was sufficient to warrant summarization.

Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AEs, a subject was counted once. If more than one occurrence of an event with in a preferred term was reported, the event of the highest severity or the worst case relationship assessment was summarized.

Clinical Laboratory Data were summarized and listed; both as laboratory values over time and change from baseline and as individual subject changes via shift tables. Vital signs were both summarized and listed. Summary statistics of raw data and change from baseline values for blood pressure, heart rate and respiration rate were presented by treatment group and time point. EKG measurements were both summarized and listed. Descriptive statistics of raw data and change from baseline values for QTc measurements were presented by time point and treatment sequence.

Concomitant Medications were listed with their start and end date, dose, frequency and route.

Bioequivalence Analysis

Analysis of variance (ANOVA) was performed on the natural log-transformed AUC_{last} , AUC_{inf} , and C_{max} for estradiol. The ANOVA model contained factors for sequence of treatments, subjects within sequence [subject (sequence)], periods and treatments was utilized to compare the effects between the test ((b) (4) ETS) and reference (Vivelle ETS) treatments. The sequence effect was tested using the subject (sequence) mean square as an error term. If a significant sequence effect was detected, only the data collected in period one were to be used for this bioequivalence analysis. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with the difference.

The natural log-transformed AUC_{last} , AUC_{inf} , and C_{max} for estradiol were analyzed for group effects by applying the ANOVA model described above. The F-statistic was used for this assessment.

The 90% confidence interval for Test/Reference ratios was constructed for baseline uncorrected and corrected estradiol C_{max} , AUC_{last} , and AUC_{84} , as well as for AUC_{inf} for corrected estradiol. Confidence intervals (90%) were estimated around ratios (test/reference) of least squares means derived from logarithmic-transformed metrics of exposure. Bioequivalence will be demonstrated if the confidence intervals (90%) for baseline uncorrected and corrected estradiol C_{max} , AUC_{last} , and AUC_{84} , as well as for AUC_{inf} for corrected estradiol fell within the range of 0.80 to 1.25. Intra-subject CV was also calculated for AUC_{last} , AUC_{84} , C_{max} and AUC_{inf} (where appropriate).

Determination of Sample Size

SAS 9.2 was used for the sample size calculation which was designed to provide sufficient statistical power for the selected primary endpoints (AUC , and C_{max}). The sample size calculation was based on the assumption of bioequivalence (BE) between the Treatment A ((b) (4) ETS/1.65 mg/ 6.6 cm²) and Reference (Treatment B: Vivelle ETS/8.66 mg /29.0 cm²) products with a ratio of geometric means equal to 0.90 (AUC) and 1.12 (C_{max}). Information from pilot study (N28-003 PK) was used to set the CV for AUC and C_{max} at 39% and 52%, respectively, using the original unit scale. A BE limit of 80-125% and a level of significance (α) of 5% were also used in this calculation.

In an equivalence test of means using two one-sided tests at a 0.05% significance level on data from a two-period cross-over design, a total sample size of 84 achieved 80.2% power when the true ratio of means was 1.12, the coefficient of variation was 0.52 on the original, unlogged scale, and the equivalence limits of the mean ratio were 80% to 125%. Assuming a dropout rate of ~20%; *the total sample size used was 100 subjects.*

Statistical analyses for peak concentration (C_{max}), and the area under the concentration time profile (AUC) were based on the two one-sided tests procedure to determine whether the average values for the pharmacokinetic measures determined after administration of the Test (Treatment A) and Reference (Treatment B) products were comparable. The average bioequivalence approach used involved the calculation of a 90% confidence interval for the ratio of the averages (population geometric means) of the measures for the Treatment A and Treatment B. *To establish bioequivalence (BE), the calculated confidence interval needed to fall within a BE limit that was set to 80-125% for the ratio of the product averages.* The anti-logs of the confidence limits obtained constituted the 90% confidence interval for the ratio of the geometric means between the Treatment A and Treatment B.

Change in the Planned Analyses

Although the protocol indicated that the statistical analysis of the bioequivalence data would include evaluation of the 90% CI for baseline uncorrected and baseline corrected estradiol Test/Reference ratios for C_{max} , AUC_{last} and AUC_{inf} , the sponsor concluded

that evaluation of the AUC_{inf} for uncorrected estradiol was *not* appropriate for an endogenously produced substance.

Reviewer's Comment

The sponsor's conclusion that evaluation of the AUC_{inf} was not appropriate was not prospectively agreed upon with the Clinical Pharmacology team.

Vivelle ETS and (b) (4) ETS are extended release transdermal drug delivery systems and since measurement of estradiol concentrations beyond the patch wear time would be confounded by endogenous estradiol, the area under the curve during the patch application period (AUC_{84}), when exogenous estradiol is predominant, is an important measure of estimating the extent of absorption of estradiol from the patch and was used in addition to AUC_{last} . As a consequence, the Test/Reference ratio for AUC_{84} was used in the primary evaluation of bioequivalence and was added to the list of parameters evaluated for baseline corrected PK parameters.

Subject 004-01-029 was excluded because the transdermal system fell off at 24 hours (Treatment A, Period 1). Subject 004-01-048 was excluded because this subject did not receive Treatment B (Period 2) due to discontinuation. Subject 004-01-063 was excluded because the pre-dose period two estradiol concentrations was nine-fold higher than pre-dose period one and the baseline levels. Subject 004-01-026 was excluded because the adjusted R-squared value for the determination of elimination rate constant for some of the treatments was less than 0.6.

DISPOSITION OF SUBJECTS

One hundred (100) post-menopausal women were enrolled and randomized to the study. All 100 completed Treatment Period 1 and 99/100 (99%) subjects completed Treatment Period 2. One subject (Subject 01-048) withdrew consent after completing the first treatment period due to a mild, unrelated AE, first degree sunburn. This subject had been randomized to treatment sequence A→B. One-hundred subjects received Treatment A ((b) (4) ETS) and 99 subjects received Treatment B (Vivelle ETS).

Protocol Deviations

Overall, there were a total of 27 protocol deviations by subject listed. Most of the deviations were related to various inclusion/exclusion criteria. Many received waivers. They include:

- four subjects (004-01-027, 004-01-028, 004-01-029, 004-01-045) who had FSH levels less than 40 mIU/mL (inclusion criterion 10), one of whom received a waiver;
- one subject (004-01-043) with a BMI of 26.8 kg/m² who received a waiver (initial inclusion criterion 5; however, this criterion was subsequently changed to 29.9 kg/m²);

- twenty-seven subjects with hematocrit values slightly below 40%, most of whom (24/27) received a waiver, and two with a hemoglobin value slightly below 12 g/dL, one of whom received a waiver (exclusion criterion 16)
- three subjects (004-01-006, 004-01-047, 004-01-077) who slightly exceeded the study defined maximum 239 g/dL for cholesterol, two of whom received waivers (exclusion criterion 17).

The remaining deviations were for the most part *out-of-window procedures*: Group 2 (12 subjects) had their breath-analyzer tests performed on Day 0 (but prior to dosing) instead of Day -1 due to equipment malfunction; four blood draws and three dermal evaluations were out of window.

In addition to the protocol deviations reported above, the majority of which were associated with inclusion/exclusion criteria during screening, there were six subjects during Treatment A (Minivelle) and eight subjects during Treatment B (Vivelle) who received Metamucil for constipation during the study (these were inconsistent with exclusion criterion 33).

The following Sponsor's table 11-1 shows the Demographic and Baseline Characteristics for Study N28-004

Table 4: Demographic and Baseline Characteristics

Parameter	Safety Population	BE Population		
		Uncorrected Estradiol [1]	Corrected Estradiol	
	N=100		C _{max} etc.[1]	AUC _{inf}
Min - max	40 - 65	40 - 65	40 - 65	40 - 65
Race				
Black or African American	8 (8.0%)	7	7	7
White or Caucasian	92 (92.0%)	90	90	89
Ethnicity				
Hispanic or Latino	97 (97.0%)	94	94	93
Not Hispanic or Latino	3 (3.0%)	3	3	3
Weight (kg)				
n	100	97	97	96
Mean (SD)	64.41 (7.232)	64.25 (7.175)	64.25 (7.175)	64.20 (7.196)
Median	64.30	64.30	64.30	64.15
Min - max	48.5 - 87.7	48.5 - 87.7	48.5 - 87.7	48.5 - 87.7
Height (cm)				
n	100	97	97	96
Mean (SD)	158.39 (5.917)	158.17 (5.875)	158.17 (5.875)	158.11 (5.875)
Median	158.00	158.00	158.00	158.00
Min - max	143.5 - 172.7	143.5 - 172.7	143.5 - 172.7	143.5 - 172.7
BMI (kg/m²)				
n	100	97	97	96
Mean (SD)	25.66 (2.340)	25.66 (2.334)	25.66 (2.334)	25.66 (2.346)
Median	25.70	25.70	25.70	25.70
Min - max	19.7 - 29.9	19.7-29.9	19.7-29.9	19.7-29.9
Gender				
n	100	97	97	96
Female	100 (100%)			

[1]For all parameters estimated except AUC_{inf}

Note, the majority of subjects in each population were White (slightly more than 90%) with the mean age and mean body weight in each population being 54 years (range from 40 to 65 years) and 64 kg (range 48 to 88 kg), respectively. The bioequivalence populations appear similar.

Extent of Exposure/Apparent Dose Released

The extent of exposure was determined by measuring the amount of residual estradiol remaining in the patches and estimating the apparent dose of estradiol released.

For the Safety population, the mean absolute amounts and percentages of applied dose absorbed from the patches were 0.45 mg and 26% and 0.43 mg and 5% for Minivelle ETS and the Vivelte ETS, respectively. The mean absolute amounts absorbed were similar; however; a much greater percentage of the drug was released from the Minivelle ETS.

Pharmacokinetic results

All 100 subjects enrolled were randomized and 99 subjects received both treatments. Two subjects did not complete both treatments: The transdermal system for Subject 004-01-029 detached from the subject's skin and was not present at 24 hours following Treatment A and Subject 004-01-048 withdrew consent prior to Treatment B administration, second treatment period. These two subjects' data were excluded from the PK analysis following Treatment A and Treatment B, respectively. In addition, due to high baseline value obtained before Treatment B administration, Subject 004-01-063 data have been excluded from summary statistics for Treatment B and the BE assessment.

Serum samples obtained were analyzed for estradiol, unconjugated estrone, and total estrone and PK analysis was performed for all three analytes. Estradiol data were analyzed with and without baseline correction.

Estradiol

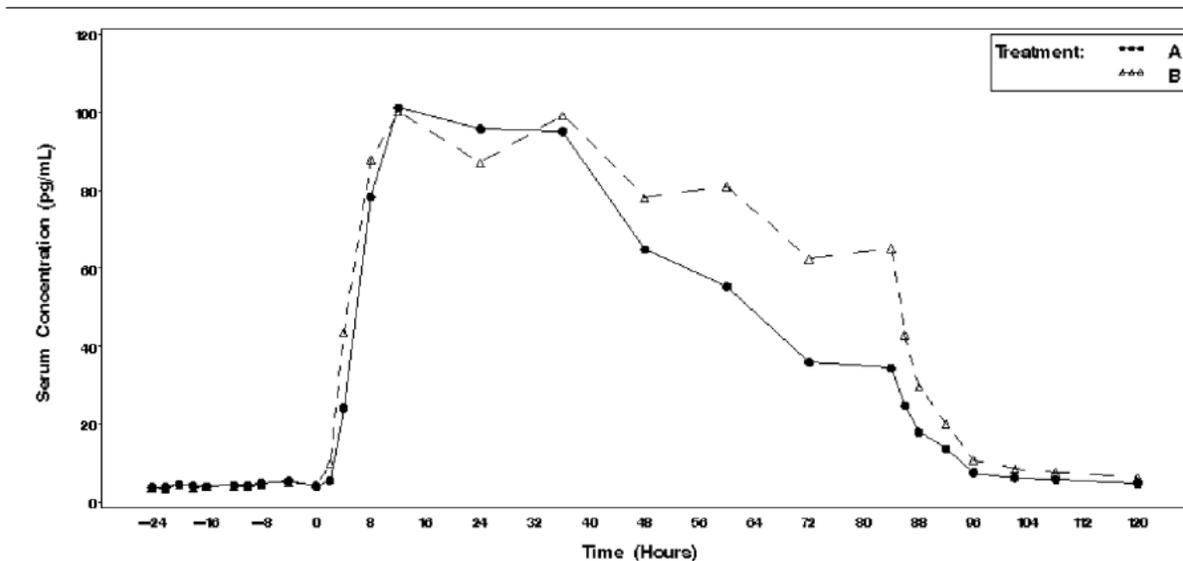
Baseline-Uncorrected Data

All but 18 baseline estradiol concentration values were above the lower limit of quantification (LLOQ) and all but two baseline values were less than 20pg/mL. The two concentration values higher than 20 pg/mL were obtained in Treatment Period two from Subject 004-01-15 (C0 = 34.9pg/mL) and Subject 004-01-63 (C0 = 89.3pg/mL). Due to the approximately 9-fold higher baseline estradiol concentration level in Treatment Period two before administration of Treatment B, the data from Subject 004-01-63 was excluded from the summary statistics for Treatment B and from the BE assessment.

The following Figures 11-1 and 11-2 and Tables 5-8 summarize the individual pharmacokinetic values for estradiol: These baseline tables and figures are for baseline uncorrected, then baseline corrected parameters are shown:

Sponsor's Figure 11-1

Figure 1: Average Baseline Uncorrected Estradiol Concentration-Time Profiles following treatment A (Test: Minivelle) and Treatment B (Reference: Vivelle)



The main PK parameters of baseline-uncorrected estradiol are summarized in the table below

Sponsor's Table 11-2

Table 5: Mean (CV) Serum PK Parameters for Baseline-Uncorrected Estradiol

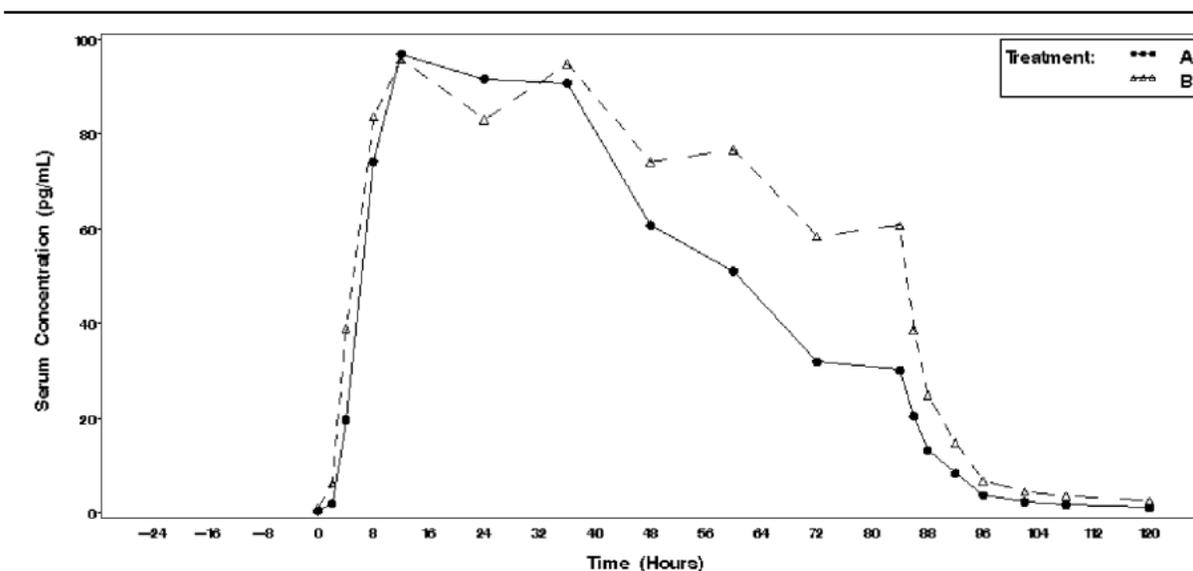
Parameter (unit)	Treatment A – Test (b) (4) ETS (N=99)	Treatment B – Reference Vivelle ETS (N = 98)
AUC ₂₄ (pg*h/mL)	5584 (37.6)	6498 (42.0)
AUC _{last} (pg*h/mL)	5939 (36.3)	7007 (40.4)
C _{max} (pg/mL)	122 (42.5)	112 (42.8)
t _{max} ‡ (hours)	24.0 (8.00 – 84.0)	24.0(8.00 – 60.0)

‡Median (minimum – maximum)

Baseline-corrected Data

The following sponsor's figure 11-2 shows the Average Baseline-corrected Estradiol concentration-Time Profiles following Treatment A (Test: Minivelle) and Treatment B (Reference: Vivelle)

Figure 2: Average Baseline-corrected Estradiol concentration-Time Profiles following Treatment A (Test: Minivelle) and Treatment B (Reference: Vivelle)



The following Sponsor's table 11-3 shows the Mean (CV) Serum PK Parameters of Baseline-Corrected Estradiol

Table 6: Mean (CV) Serum PK Parameters of Baseline-Corrected Estradiol

Parameter (unit)	Treatment A – Test (b) (4) ETS (N=99)	Treatment B – Reference Vivelle ETS (N = 98)
AUC ₈₄ (pg*h/mL)	5231 (40.2)	6151 (45.1)
AUC _{last} (pg*h/mL)	5431 (39.7)	6505 (44.4)
AUC _{inf} (pg*h/mL)	5461 (39.5)	6522 (44.3)
C _{max} (pg/mL)	118 (52.1)	108 (48.7)
t _{max} † (hours)	24.0 (8.00 – 84.0)	24.0 (8.00 – 60.0)
t _{1/2} (hours)	6.15 (43.3) †	5.88 (30.9)

† Median (minimum – maximum)

† N = 98 (Subject 004-001-026 is missing AUC_{inf} due to r²_{adjusted} < 0.6)

Reviewer's Comment

Note that for baseline uncorrected and corrected E₂ values the reference product Vivelle serum levels appear higher than Minivelle from the 48 hour of release until roughly the 88-96 hour period. From a clinical viewpoint this may be important in subjects with respect to their obtaining relief of symptoms over the initial 3-4 day period at this lowest dose.

The sponsor presented similar tables and figures for estrone. This data show similar (as with estradiol) serum levels of estrone with the Vivelle always showing higher levels than Minivelle ((b) (4))

The following Sponsor's table 11-5 shows the Mean (CV) Serum PK Parameters of Total Estrone

Table 7: Mean (CV) Serum PK Parameters of Total Estrone

Parameter (unit)	Treatment A – Test (b) (4) (N=99)	Treatment B – Reference Vivelle (N = 98)
AUC ₈₄ (pg*h/mL)	74611 (60.04)	79421 (57.11)
AUC _{last} (pg*h/mL)	89748 (62.31)	99582 (59.13)
C _{max} (pg/mL)	1329 (54.24)	1314 (59.83)
t _{max} * (hours)	36.00 (24.00 – 92.00)	48.00 (12.00 – 102.0)

*Median (minimum – maximum)

The following Sponsor's table 11.6 shows the Statistical Analyses of Uncorrected and Corrected Estradiol PK Parameters

Table 8: Statistical Analyses of Uncorrected and Corrected Estradiol PK Parameters

	Comparison		LSM Difference- Log Scale LSM (SE)	Test/Reference Ratio Mean	90% CI for Test/Reference Ratio of Mean
	Test (A) N=97	Reference (B) N= 97			
Uncorrected Estradiol					
C _{max} (pg/mL)	4.71 (0.0445)	4.62 (0.0445)	0.0840 (0.0346)	1.09	1.03 - 1.15
AUC ₈₄ (pg*hr/mL)	8.55 (0.0429)	8.69 (0.0429)	-0.139 (0.0364)	0.870	0.819 - 0.925
AUC _{last} (pg*hr/mL)	8.62 (0.0414)	8.77 (0.0414)	-0.154 (0.0361)	0.858	0.808 - 0.911
Corrected Estradiol					
C _{max} (pg/mL)	4.66 (0.0471)	4.57 (0.0471)	0.0893 (0.0363)	1.09	1.03 - 1.16
AUC ₈₄ (pg*hr/mL)	8.47 (0.0465)	8.62 (0.0465)	-0.146 (0.0388)	0.864	0.810 - 0.922
AUC _{last} (pg*hr/mL)	8.51 (0.0460)	8.68 (0.0460)	-0.164 (0.0394)	0.849	0.795 - 0.906
AUC _{inf} (pg*hr/mL)	8.52 (0.0458)	8.69 (0.0458)	-0.173 (0.0390)	0.842	0.789 - 0.898

Reviewer’s Comment

This summary table shows that rate and exposure (C_{max} and AUC) is similar for Minivelle and Vivelle. For the 90% CI test/reference ratio of the mean corrected E₂ serum levels the AUC₈₄ for Minivelle is bioequivalent to Vivelle. Note that the AUC_{last} and AUC_{inf} do not demonstrate bioequivalence at the 90% CI for the test/reference ratio of the mean. The sponsor states that the most relevant of the AUC_s is the AUC₈₄ because it more adequately reflects the extent of absorption from extended release formulations like Vivelle and Minivelle with minimum interference of endogenous estradiol. In addition, the approved label states the application should be applied every 3-4 days, meaning that as long as the patch is adhered to the skin for a consistent period of 72 to 96 hours, serum levels are maintained. In another scenario, if the patch were applied only once and not repetitively, the AUC_{last} and AUC_{inf} would be more clinically relevant. Therefore, from a clinical viewpoint, this reviewer believes the most relevant of the AUCs is the AUC₈₄ measurement.

Safety Evaluation

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths or other serious adverse events occurred during the trial. During the washout period and while not confined to the clinic, one subject, 01-048, experienced a

mild, unrelated AE of first-degree sunburn, which led to withdrawal from the study. A narrative for this subject follows below:

This 56 year old, 60.9 kg, White female of Hispanic/Latino ethnicity with a medical history of menopause and a number of surgeries (two cesarean sections, hysterectomy, abdominoplasty, and mammoplasty), who signed consent for study 28-004 study on February 25, 2011 and was randomized to treatment regimen AB.

The subject received her first dose of study product on March 8, 2011 [Treatment A (test): Minivelle ETS at 08:18. She reported a mild AE of hot flush on the day of treatment which resolved on the same day and did not result in a change of treatment. She was due to receive the reference treatment, Vivelle ETS on Day 22 (March 29, 2011) but *was not dosed* due to first degree burn on the abdomen which was reported with an onset date of March 27, 2011 and a stop date of March 30, 2011.

The Investigator evaluated this adverse event as mild in severity and unrelated to treatment. Her vital signs, safety lab and ECG results were normal throughout the study, with the exception of an elevated cholesterol level at both screening and the end of the study.

Adverse Events

The following sponsor's table 12-1 summarizes adverse events for the two treatment groups

Table 9: Adverse Events for the Two Treatment Groups

	Treatment A		Treatment B	
	(b) (4) ETS (N=100)		Vivelle ETS (N=99)	
	Subjects n (%)	Events	Subjects n (%)	Events
Subjects who experienced ≥ 1 adverse event	26 (26%)	34	35 (35.4%)	43
Subjects who experienced ≥ 1 adverse event assessed as possibly related to study drug	22 (22%)	25	30 (30.3%)	35
Subjects who experienced an adverse event leading to withdrawal of study drug	1 (1%)	1		

Twenty-six percent of subjects experienced a total of 34 AEs during Treatment A (Minivelle) as compared to 35.4% experiencing a total of 43 AEs for subjects using

Vivelle ETS. All AEs were reported as mild in intensity and most were deemed possibly related to treatment. During the washout period, while not confined in the clinic, subject 01-048 (reviewed above) experienced an AE of first degree sunburn, which led to her withdrawal from the study.

The following sponsor's table 12-2 summarizes Possibly Treatment-Related TEAE, Safety Population

Table 10: Summary of Possibly Treatment-Related TEAE, Safety Population

System Organ Class/ Preferred Term	^{(b) (4)} ETS (N=100)		Vivelle ETS (N=99)	
	Subjects n (%)	Events	Subjects n (%)	Events
Gastrointestinal Disorders	6 (6.0%)	6	11 (11.1%)	11
Abdominal Pain	3 (3.0%)	3	4 (4.0%)	4
Constipation	3 (3.0%)	3	7 (7.1%)	7
General Disorders And Administration Site Conditions	0	0	1 (1.0%)	1
Pain	0	0	1 (1.0%)	1
Musculoskeletal And Connective Tissue Disorders	5 (5.0%)	5	5 (5.1%)	5
Back Pain	3 (3.0%)	3	2 (2.0%)	2
Pain In Extremity	2 (2.0%)	2	3 (3.0%)	3
Nervous System Disorders	6 (6.0%)	6	10 (10.1%)	10
Dizziness	0	0	1 (1.0%)	1
Headache	6 (6.0%)	6	9 (9.1%)	9
Reproductive System And Breast Disorders	2 (2.0%)	2	2 (2.0%)	2
Breast Tenderness	0	0	2 (2.0%)	2
Vaginal Discharge	2 (2.0%)	2	0	0
Vascular Disorders	6 (6.0%)	6	6 (6.1%)	6
Hot Flush	6 (6.0%)	6	6 (6.1%)	6
Number of Subjects with ≥1 Possibly Related TEAE	22 (22%)	25	30 (30.3%)	35

Reviewer's Comment

Although slightly more subjects in Treatment B than in Treatment A experienced possibly related treatment emergent adverse events (TEAEs) (approximately 30% vs. 20%), the distribution by system organ class (SOC) and preferred term (PT) appear similar and are not concerning for an estrogen product.

Patch Adhesion

Following both Treatment A (Minivelle ETS) and Treatment B (Vivelle ETS) 99% of subjects had adhesion scores of 0 ($\geq 90\%$ adhered) at the 84 hour time point. There was one Treatment A subject (1/100 or 1.0%) whose patch became detached during the 24- hour time point and there were two Treatment A subjects whose adhesion scores were ≥ 2 ($\geq 50\%$ $< 75\%$ adhered). There were no patch detachments in Treatment B (Vivelle ETS); there were two subjects whose patch showed adhesion of $\geq 75\%$ to $< 90\%$. The difference in adhesion between Treatments A and B for percent adherence was *not* statistically significant

Skin Irritation Evaluation

Prior to dosing, for Treatment A (Minivelle ETS), no evidence of skin irritation was observed. At the first post-dosing time point of 84 hours (just prior to patch removal) 1/100 (1%) subjects experienced grade 2 erythema (definite erythema, readily visible; minimal edema or minimal papular response) while at the 84 hour post-patch removal time point, 30/100 (30%) experienced grade 1 erythema (very slight erythema, barely perceptible) or grade 2 erythema. At the subsequent time points of 85, 96, 108, and 120 hours, the incidences of subjects with grade 1 or grade 2 erythema decreased to 21/100 (21%), 4/100 (4%), 2/100 (2%) and 1/100 (1%), respectively, for Treatment A.

Prior to dosing, for Treatment B (Vivelle ETS), there were no subjects with evidence of skin irritation. At the first post-dosing time point of 84 hours (just prior to patch removal) 14/99 (14%) subjects experienced grade 1 or grade 2 erythema while at the 84 hour post-patch removal time point, 88/99 (89%) experienced grade 1 or grade 2 erythema. At the subsequent time points of 85, 96, 108 and 120 hours, the incidences of subjects with grade 1 or grade 2 erythema decreased to 61/99 (62%), 26/100 (26%), 19/100 (19%) and 7/100 (7%), respectively, for Treatment B.

Overall, Treatment A had 35/100 (35%) subjects who experienced grade 1 erythema and 2/100 (2%) experienced grade 2 erythema; Treatment B had 86/99 (87%) subjects who experienced grade 1 erythema and 20/99 (20%) who experienced grade 2 erythema. The overall mean cumulative irritation scores were 0.09 for Treatment A and 0.35 for Treatment B. There were no patches removed due to unacceptable irritation in either treatment group.

Reviewer's Comment

The higher rate of skin irritation with the larger Vivelle patch is not unexpected and overall the irritation profile was recorded as mild.

Adhesive Residue

Following Treatment A (Minivelle ETS), 12% (12/100) and 88% (88/100) of subjects had no residue or light residue at the time of patch removal, respectively. Following Treatment B (Vivelle ETS), 2% (2/99), 97% (96/99) and 1% (1/99) of subjects had no residue, light residue, and moderate residue at the time of patch removal, respectively.

Experience of Discomfort

All subjects in Treatments A and B reported no discomfort except at the final time point of application. At the final time point (84 hours) one subject in Treatment A reported mild discomfort.

Evaluation of Laboratory Parameters

Laboratory parameters (hematology, clinical chemistry, urinalyses) were measured at screening (baseline) and at the last visit. Summaries were prepared of descriptive statistics, changes from baseline to the last visit, values outside the normal range, and shifts from baseline to the last visit.

Hematology Parameters

For most of the parameters (Hematocrit, Hemoglobin, platelets, leukocytes, etc), the number of abnormal values remained the same or were reduced from baseline to the last visit. At the last visit the number of abnormal hematocrit values increased from four at baseline to 14; the number of abnormal hemoglobin values increased from three at baseline to 20 at the last visit. Platelets and Leukocytes did not vary significantly.

Chemistry Parameters

There were no remarkable changes in the mean values (SD) for the chemistry parameters. With the exception of cholesterol; all mean values were within normal ranges and the standard deviations were similar between the two time points. The cholesterol means slightly exceeded the upper bound of normal, i.e., 205 vs. 200, at baseline and decreased to 202 at the last visit.

Urinalysis Parameters

The number of abnormal values was reduced from baseline to the last visit; however, there were several exceptions. For the bacteria in the urine the number of subjects with abnormal numbers increased from five at baseline to seven at the last visit; for nitrite, the number of abnormal values increased from four at baseline to 11 at the last visit and for specific gravity the number of abnormal values increased from four at baseline to eight at the last visit.

Vital Signs

There were no Clinically significant abnormal recordings regarding systolic blood pressure, diastolic blood pressure, heart rate, EKG or weight change from baseline to end of treatment.

Reviewer's Comment

There are no new safety concerns observed during this short term study. The adverse events attributed to use of Minivelle and Vivelle were similar and well tolerated. Skin irritation with Minivelle was slightly less than with Vivelle and patch adhesion appears better than with Vivelle (smaller patches usually exhibit greater adhesion and less irritation).

Study N28-005

This was a Phase I, open-label, single-center, randomized, single-dose, three-way crossover study in 36 healthy, non-smoking postmenopausal women (aged 40 to 65 years, inclusive). Subjects were housed during treatment period one from approximately 36 hours prior to dosing through the 120-hour post-dose assessment. During treatment periods two and three subjects were housed from approximately 12 hours prior to dosing through the 120- hour post-dose assessments.

Each subject received a single dose of each of the three treatments. Each transdermal system was worn for 84 hours. There was a minimum washout period of at least 14 days between the 120-hour assessments of one treatment and the administration of the second treatment. Eligible subjects reported to the clinical research unit (CRU) on Day -1, Day 21, and Day 42 in the evening at approximately 1900 hours and were housed in the CRU until their release following completion of the 120-hour blood collection.

The three treatments administered in this study were:

- **Treatment A** (Test 1): one 84-hour application of the 1.65 mg/6.6 cm² (b) (4) ETS
- **Treatment B** (Test 2): one 84-hour application of the 0.827 mg/3.3 cm² (b) (4) ETS
- **Treatment C** (Test 3): one 84-hour application of the (b) (4) (b) (4) ETS

The administration sequence of the three treatments was performed according to a Randomization Schedule. Randomization was performed prior to the first study treatment administration (Day 7).

- The trial consisted of the following four segments:
- A screening period (maximum duration of 21 days),

- The treatment period (48 days in duration),
- End of study (or Early Termination),
- Follow up visit (7-10 days after end of study).

A full schedule of activities is shown in sponsor's table 9-1 in the Appendix.

Screening Period

Thirty-six healthy, postmenopausal women meeting all the eligibility criteria were selected for the study within three weeks of the first treatment administration. The sponsor's table 9-1, in the N28-005 study report, provides a list of procedures performed. The reader is referred to that table.

Inclusion Criteria

Inclusion criteria are identical to study N28-004

Exclusion Criteria

Exclusion criteria are identical to study N28-004 with an addition of #39 where subjects who had used antihistamines or topical drugs at the patch site within 72 hours prior to receiving the first dose of study medication were excluded.

Blinding

This trial was an open label study designed to evaluate dose proportionality in which all subjects received all treatments. Since no placebo was used and the three ETSs were three different sizes, blinding was not feasible or necessary given the nature of the study.

Pharmacokinetic, Dermal, and Safety Measurements Assessed

See study N28-004 for all pharmacokinetic, dermal and safety measurements assessed during this study.

See study N28-004 for dermal evaluations, adhesion, patient discomfort and irritation scores.

Disposition of Subjects

Thirty-six (36) post-menopausal women were enrolled and randomized to the study. All 36 completed all three periods. Twelve (12) subjects each received Treatment A ((b) (4) ETS: 1.65 mg/6.6 cm²), Treatment B ((b) (4) ETS: 0.827 mg/3.3 cm²)

or Treatment C ((b) (4) ETS: (b) (4)) in each of the three periods and all 36 subjects completed the study.

Protocol deviations were captured in two places for this study – in a deviations log at the site and as deviations to PK sampling times recorded in the eCRF.

In the site deviations log, there were three deviations related to inclusion criteria and 11 deviations related to the exclusion criteria. The three inclusion criteria deviations all related to inclusion criterion 6 and the requirement that endometrial thickness be less than 5 mm. Three subjects had endometrial thicknesses of exactly 5 mm and were admitted and dosed without first informing Noven.

The 11 exclusion criteria deviations all related to exclusion criterion 16 which excluded subjects with a hematocrit of less than 40. Eleven subjects had hematocrit values ranging from 37.2 to 39.9. Three of these were admitted without a waiver, the remaining eight were granted waivers by the Noven Medical monitor.

Most of the remaining deviations in the site log were out-of-window blood draws for PK although there was one procedural deviation related to a failure to take blood pressure measurements on the same arm each time.

Data from the eCRF indicate that the majority of subjects had one or more deviations in PK sampling time. The vast majority of these deviations were 5 minutes or less and one subject had a deviation that exceeded 10 minutes.

Demographics

All subjects were post-menopausal White or Caucasian and Hispanic or Latino females with the population mean age and mean body weight being 55 years (range from 49 to 65 years) and 68 kg (range 53 to 82 kg), respectively.

Results

The extent of exposure was determined by measuring the amount of residual estradiol remaining in the patches and estimating the apparent dose of estradiol released.

The mean absolute amounts (percentages of applied dose absorbed) from the patches were 0.43 mg (25.3%), 0.241 mg (28%), and 0.127 mg (29.5%) for Treatment A ((b) (4) ETS: 1.65 mg/ 6.6 cm²), Treatment B ((b) (4) ETS: 0.827 mg/ 3.3 cm) and Treatment C ((b) (4) ETS: (b) (4)) respectively. The mean absolute amounts absorbed were proportional to dose and the percentages absorbed were very similar across the three treatments.

All but 12 baseline uncorrected estradiol concentration values were above the LLOQ and all baseline values were less than 20 pg/mL. All subjects had measurable estradiol concentrations following all three treatments administered.

The main PK parameters of baseline uncorrected estradiol is summarized in the following sponsor's table 11-2 below:

Table 11: Mean (CV%) Serum PK Parameters for Baseline-Uncorrected Estradiol

Parameter (unit)	Treatment A 1.65 mg / 6.6 cm ² (N=36)	Treatment B 0.827 mg / 3.3 cm ² (N = 36)	Treatment C (b) (4) (N = 36)
AUC ₀₋₈₄ (pg*h/mL)	5875 (31.6)	3057 (32.1)	1763 (34.0)
AUC _{0-last} (pg*h/mL)	6252 (31.0)	3320 (31.3)	1979 (32.7)
C _{max} (pg/mL)	117 (33.5)	56.6 (31.1)	30.3 (36.7)
t _{max} ‡ (hours)	24.0 (8.00 – 60.0)	24.0 (8.00 – 60.0)	36.0 (8.00 – 84.0)

‡Median (minimum – maximum)

Baseline-corrected Data

The individual pharmacokinetic parameters obtained for *baseline-corrected* estradiol by non-compartmental analysis are summarized in the following sponsor's table 11-3:

Table 12: Mean (CV%) Serum PK Parameters for Baseline-Corrected Estradiol

Parameter (unit)	Treatment A 1.65 mg / 6.6 cm ² (N=36)	Treatment B 0.827 mg / 3.3 cm ² (N = 36)	Treatment C (b) (4) (N = 36)
AUC ₀₋₈₄ (pg*h/mL)	5586 (33.2)	2769 (34.7)	1475 (38.9)
AUC _{0-last} (pg*h/mL)	5836 (33.1)	2905 (34.5)	1565 (38.7)
AUC _{0-inf} (pg*h/mL)	5855 (33.1)	2937 (34.5) ^a	1603 (37.7) ^b
C _{max} (pg/mL)	114 (39.0)	53.0(32.6)	26.8(40.2)
t _{max} ‡ (hours)	24.0 (8.00 – 60.0)	24.0 (8.00 – 60.0)	36.0 (8.00 – 84.0)
t _{1/2} (hours)	7.90 (32.5)	7.81 (47.7)	7.01(32.5)

^aN=35 (Subject 005-001-034 is missing AUC_{inf} due to r²_{adjusted} < 0.6)

^bN=34 (Subjects 005-001-027 and 005-001-034 are missing AUC_{inf} due to r²_{adjusted} < 0.6)

‡Median (minimum – maximum)

The following sponsor's table 11-5 shows the baseline uncorrected serum PK parameters for total estrone.

Table 13: Mean (CV%) serum PK Parameters for Total Estrone

Parameter (unit)	Treatment A 1.65 mg / 6.6 cm ² (N=36)	Treatment B 0.827 mg / 3.3 cm ² (N = 36)	Treatment C (b) (4) (N = 36)
AUC ₀₋₈₄ (pg*h/mL)	75977 (59.53)	44538 (58.29)	31605 (54.95)
AUC _{0-last} (pg*h/mL)	90914 (60.50)	55405 (59.83)	40639 (55.75)
C _{max} (pg/mL)	1394 (59.00)	763.4 (59.63)	524.7 (59.58)
t _{max} † (hours)	48.0 (24.00 – 60.00)	48.0 (24.00 – 72.0)	48.0 (24.00 – 60.00)

†Median (minimum – maximum)

In reviewing the data for uncorrected estradiol (shown above), unconjugated estrone (data not shown), and total estrone (shown above) concentration-time profiles, it appears that the mean baseline uncorrected estradiol, unconjugated estrone, and total estrone concentration-time profiles indicate metabolite concentrations closely correlate with the parent concentrations following all three dose strengths. The most variability was observed with total estrone. The inter-individual variability for C_{max} and the AUCs was approximately 60% for total estrone while for estradiol and unconjugated estrone, the variability was approximately 30%. Somewhat more variability was observed in the estradiol PK parameters following the lowest dose than in the mid and high doses.

The following sponsor's table 14.2.1.3 shows the mixed effects Power Models for C_{max}, AUC_{inf}, AUC_{last}, and AUC₀₋₈₄ of corrected estradiol were used to assess pharmacokinetic dose proportionality.

Table 14: Mixed Effects Power Models for C_{max}, AUC_{inf}, AUC_{last}, and AUC₀₋₈₄ of corrected estradiol used to assess pharmacokinetic dose proportionality.

	Parameter β Estimate (90% CI)
Corrected Estradiol C _{max} (pg/mL)	1.0546 (1.0123, 1.0970)
AUC _{0-1st} (pg hr/mL)	0.9665 (0.9143, 1.0187)
AUC _{1st-2st} (pg hr/mL)	0.9688 (0.9190, 1.0186)
AUC ₀₋₈₄ (pg hr/mL)	0.9793 (0.9311, 1.0274)

Reviewer's Comment

The estimates for parameter β are entirely within the pre-specified range of (0.84, 1.16). Therefore dose-proportionality is demonstrated.

Safety Evaluation

Adhesion

Following Treatment A (Minivelle ETS: 1.65 mg/6.6 cm²), Treatment B (Minivelle ETS: 0.827 mg/3.3 cm²) and Treatment C (Minivelle ETS: [REDACTED] (b) (4)) almost all (35/36 for Treatment A and B and 36/36 for Treatment C) subjects had adhesion scores of 0 ($\geq 90\%$ adhered) at all-time points and there were no subjects in any treatment group with adhesion scores above 1 ($\geq 75\% < 90\%$ adhered). From the 36 hour time point to removal of the system (the 84 hour time point), there was one subject in Treatment A (Minivelle ETS: 1.65 mg/6.6 cm²) with an adhesion score of 1. There was also one subject in Treatment B (Minivelle ETS: 0.827 mg/3.3 cm²) with an adhesion score of 1 but that occurred at the last time point. There were no subjects whose ETS became completely detached and the mean duration of ETS wear was the same (84.0 hours) for all three treatments.

Residue

Following any of the three treatments, about 69% to 83% of subjects had adhesive residue scores of 0, indicating no residue, and the remaining subjects had scores of 1, indicating light residue at the time of ETS removal.

Treatment C (Minivelle ETS: [REDACTED] (b) (4)) had the greater number of subjects with no residue (30/36, 83%), followed by Treatment B (Minivelle ETS: 0.827 mg/3.3 cm²) and Treatment A (Minivelle ETS: 1.65 mg/6.6 cm²) with 29/36 (81%) and 25/36 (69%), respectively.

Irritation

Prior to dosing, no evidence of skin irritation was observed in any of the three treatment groups. This was true at the 84 hour time point (just prior to ETS removal) with the exception of a one subject in Treatment B whose skin showed a slightly glazed appearance. Following ETS removal, 92% to 97% of the subjects in each treatment group experienced no or minimal irritation across the remaining time points (85, 96, and 108 hours). Mild skin irritation (grade 1 erythema) was reported at 85-hour time point with incidences of 30.6%, 22.2 % and 25.0 % in Treatment A (Minivelle ETS: 1.65 mg/ 6.6 cm²); Treatment B (Minivelle ETS: 0.827 mg/ 3.3 cm²); and Treatment C (Minivelle ETS: [REDACTED] (b) (4)) respectively. Mild skin irritation (grade 1 erythema) was reported at 96 hour time point with incidences of 25.0%, 22.2 % and 13.9 % in Treatment A (Minivelle ETS: 1.65 mg/ 6.6 cm²), Treatment B (Minivelle ETS: 0.827 mg/ 3.3 cm²) and Treatment C (Minivelle ETS: [REDACTED] (b) (4)) respectively. Mild skin irritation (grade 1 erythema) was also reported at 108 hour time point with incidences of 8.3%, 13.9 % and 11.1 % in Treatment A (Minivelle ETS: 1.65 mg/ 6.6 cm²), Treatment B (Minivelle ETS: 0.827 mg/ 3.3 cm²) and Treatment C (Minivelle ETS: [REDACTED] (b) (4)), respectively.

Grade 2 scores (definite erythema) were only seen at the 85 hour time point (just after ETS removal) when this score was recorded for 2/36 (5.6%), 3/36 (8.3%), and 1/36 (2.8%) subjects in Treatment A (Minivelle ETS: 1.65 mg/6.6 cm²), Treatment B (Minivelle ETS: 0.827 mg/3.3 cm²) and Treatment C (Minivelle ETS: (b) (4)), respectively. Across the study there were no subjects who had a combined irritation score of 3 or who had an ETS removed due to unacceptable irritation.

Discomfort

Across all time points, subjects in Treatment B (Minivelle ETS: 0.827 mg/3.3 cm²) and Treatment C (Minivelle ETS: (b) (4)) reported no discomfort. For Treatment A, (Minivelle ETS: 1.65mg/6.6cm²) there were two subjects (01-022 and 01-031) who reported mild discomfort. Subject 005-01-031 reported mild discomfort at 12 and 36 hours and Subject 005-01-022 reported mild discomfort at the final time point of 84 hours.

Adverse Events

No deaths or SAEs occurred during the study and no subjects were withdrawn from the study due to an AE.

The following sponsor's table 12-1 gives a summary of treatment emergent adverse events (TEAEs) and whether these events were deemed possibly related.

Table 15: Summary of Adverse Events Study N28-005

	Treatment A		Treatment B		Treatment C	
	1.65 mg/6.6 cm ² (N=36)		0.827mg/3.3 cm ² (N=36)		(b) (4) (N=36)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
Subjects who experienced ≥ 1 adverse event	11 (31%)	19	11 (31%)	14	10 (28%)	25
Subjects who experienced ≥ 1 AE assessed as						
Probably related	4 (11%)	5	3 (8%)	3	6 (17%)	7
Possibly related	6 (17%)	12	5 (14%)	6	1 (3%)	14

All adverse events were mild in severity and the majority was assessed by the investigator as related (either possibly or probably) to study treatment. There was no dose relationship to any drug-related adverse event. The most frequent drug-related adverse events were back pain (possibly-related; 1.65mg 5.6%; 0.827, 2.8%; (b) (4))

(5.6%) and lower abdominal pain (probably-related: 1.65mg, 8.3%; 0.827, 2.8%; (b) (4) 2.8%).

Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 16: Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I	N28-001	5.3.1.1	Primary: <ul style="list-style-type: none"> To determine the relative bioavailability of (b) (4) formulations to Vivelle To determine the wear characteristics these transdermal systems 	Randomized, single center, open label, single center, 3 way cross-over with 7 day wash out period in between	Treatment A: One (b) (4) applied for 84 hours Treatment B: One (b) (4) applied for 84 hours Treatment C: One 8.66 mg/29 cm ² Vivelle applied for 84 hours.	26	Healthy Postmenopausal women	84 hours	Completed Full Clinical Study Report

Clinical Review
 Phill H. Price, M.D.
 NDA 203752
 Minivelle (estradiol transdermal delivery system)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I	N28-003	5.3.1.2	Primary <ul style="list-style-type: none"> To assess the BE of the 2 (b) (4) formulations To assess the wear characteristics of the 2 (b) (4) formulations To assess the safety and tolerability of the 2 (b) (4) formulations 	Randomized, open-label, single-center, single-dose, 3-treatment, 3-period crossover study with at least a 7 day wash out period in between	Treatment A: One (b) (4) applied for 84 hours Treatment B: One (b) (4) applied for 84 hours Treatment C: One 8.66 mg/29 cm ² Vivelle applied for 84 hrs.	18	Healthy Postmenopausal women	84 hours	Completed Full Clinical Study Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I	N28-005	5.3.3.1	Primary: <ul style="list-style-type: none"> To assess the dose proportionality of (b) (4) in healthy postmenopausal women. Secondary: <ul style="list-style-type: none"> To assess wear characteristics of the transdermal systems. To assess safety and tolerability of the transdermal systems. 	Randomized, single-center, open-label, single-dose, three-way crossover study with three treatments and three treatment periods with a minimum 21-day washout period between treatment administrations.	Treatment A: One 1.65 mg/6.6 cm ² (b) (4) applied for 84 hours. Treatment B: One 0.827 mg/3.3 cm ² (b) (4) applied for 84 hours. Treatment C: One (b) (4) applied for 84 hours.	36	Healthy Post-Menopausal Women	84 hours	Completed; Full Clinical Study Report

5.2 Review Strategy

The previous sections of this review have focused on the pivotal PK study N28-004 (see Section 4.43). This study was designed to demonstrate that Minivelle is bioequivalent to Vivelle. In addition, study N28-005 was designed to demonstrate that Minivelle dose-proportionality of three dosages of Minivelle, the 1.65 mg/6.6cm², the 0.827mg/3.3 cm² and the [REDACTED] (b) (4) patches, respectively. Subsequent Section 6 Review of Efficacy and Section 7 Review of Safety in this review will discuss the original clinical trial data under NDA 20-323 that is bridged via the BE study to support efficacy and safety of Minivelle.

5.3 Discussion of Individual Studies/Clinical Trials

No new safety and efficacy data from clinical trials are submitted with this NDA.

6 Review of Efficacy (this section will present a historical summary of previously reviewed data)

Efficacy Summary

There is no primary efficacy data for review with this NDA. A short synopsis of the original clinical trial data from Vivelle will be presented. Vivelle (NDA 20-323) was initially approved in October 1994. The doses sought for approval were 0.0375mg, 0.05mg, 0.075mg, and 0.1mg of estradiol per day. In the initial review cycle the 0.075 and 0.1 mg per day doses demonstrated efficacy at weeks 4 through week 12. The 0.050mg dose did not demonstrate efficacy at week 4 and 12. The efficacy of the 0.050mg/day dose was accepted based on bioequivalence to another estradiol transdermal system. The Vivelle 0.0375mg/day did not demonstrate efficacy until the sixth treatment week. Therefore, the 0.0375mg dose was approved in October 1994 with restrictive language stating that women taking the 0.035mg/day dosage may experience a delay in the onset of efficacy.

A phase 4 study was submitted under on April 30, 1999 under Supplement 021. Supplement 021 was approved on April 25, 2000. Supplement 021 addressed the sponsor's original Phase 4 commitment dated March 24, 1994. The Phase 4 study was a randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of the 0.0375mg/day dose of Vivelle; approximately 259 subjects were enrolled. The sample size was sufficient to detect a mean difference of 2.0 in the total number of hot flushes per day. In cycle 1 the mean difference was -3.0 (ITT) and this was maintained through cycles 2 and 3 (-3.59 with a p-value of <0.001. Severity was also statistically significant different in cycles 2 and 3. This supplement provided evidence that the lowest dose of Vivelle 0.0375mg/day was statistically significant different from placebo

(and the statistical difference was clinically meaningful) at the end of weeks 4, 8 and 12 in the treatment of moderate to severe vasomotor symptoms.

6.1 Indication

Treatment of Moderate to Severe Vasomotor Symptoms

6.1.1 Methods

The original efficacy data for Vivelle (studies 1003A and 1003B) are summarized. In addition, Supplement 021 is also reviewed. This supplement, reviewed in 1999, supported the efficacy of the 0.0375 mg/day dose.

6.1.2 Demographics

The sponsor conducted two randomized, multi-center, double blind, placebo controlled parallel group Phase 3 studies (1003A and 1003B) designed to evaluate the safety and efficacy of the Noven estradiol transdermal delivery system (EDTS) against placebo in the treatment of estrogen deficiency states. The studies were designed to have an 8-week run in period which included a 4-week placebo period and 12 weeks of active treatment. In study 1003A placebo was compared to four doses (0.0375, 0.05, 0.075, and 0.1mg/day) of the Noven patch, while in study 1003B two doses (0.0375, 0.1mg/day) were compared to placebo.

Study 1003A

In study 1003A, 234 subjects were randomized to treatment groups at 11 centers in the US. There were 45 subjects in the EDTS 0.0375mg/day group, 50 subjects in the 0.050mg/day group, 46 subjects in the 0.075mg/day group, 44 subjects in the 0.01mg/day group, and 49 subjects in the placebo group. Of the 234 subjects enrolled, 216 (92.3%) were white, 13 (5.5%) were black and 5 (1.9%) were "other".

6.1.3 Subject Disposition

The following table from the primary medical officer (MOR) shows the subject disposition for Study 100A

Table 17: Subject Disposition for Study 1003A

Treatment Groups	Visit 4	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12
Noven 0.0375mg/day	45	44	43	43
0.05mg/day	50	50	49	48

0.075mg/day	46	44	43	43
0.1mg/day	44	43	41	36
Placebo	49	46	41	41

Treatment Diaries were reviewed at weeks 1, 4, 8, and 12

Inclusion Criteria were:

- Normal healthy women between the ages of 21 and 65, who have experienced menopause for one year prior to enrollment or women who have undergone a bilateral oophorectomy no less than 2 months prior to enrollment;
- Women with moderate to severe vasomotor symptoms, specially a minimum of *six hot flashes per day* based on the average number of hot flashes during the two weeks of placebo run-in phase (Amendment V);
- Results of the vaginal examination were consistent with menopausal status;
- Baseline estradiol (E₂) levels < 20 pg/ml; FSH levels >50 mIU;
- Mammography acceptable within the prior three months
- EKG and Papanicolau (PAP) smear clinically acceptable;
- Written informed consent.

Reviewer's Comment

In this study, the baseline entry criteria of six hot moderate to severe hot flashes is below the Division's recommendations of seven to eight moderate to severe hot flashes.

Exclusion criteria were:

- Non-menopausal women and women in whom the menopause began less than one year earlier, except for those who have undergone oophorectomy as specified in item 1a or the inclusion criteria
- Women with known or suspected malignancies or other serious diseases;
- Allergic dermatitis or eczema;
- Undiagnosed vaginal bleeding;
- History of documented active thrombophlebitis or thromboembolic disorders;
- Uncontrolled hypertension with a diastolic blood pressure >115 mmHg;
- Uncontrolled diabetes mellitus;
- Clinically significant renal or hepatic abnormalities;
- Hypercalcemia;
- The following concomitant medications: clonidine, anti-epileptics, antidepressants or tranquilizers, any other hormonal therapy, ergotamine and its derivatives;
- Use of reproductive steroids, hormones, Premarin[®], or other conjugated equine estrogens within 60 days before randomization;
- Use of any investigational drug within 30 days before start of the study;
- Women who may be regarded as unreliable for this study; and
- History of alcohol or drug abuse in the year preceding study entry.

Reviewer’s Comment

Inclusion and exclusion criteria are similar to criteria used for review of more contemporary estrogen-estrogen/progestin products with the exception of six hot moderate to severe hot flashes.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy parameter was a reduction in the mean number of hot flashes. The efficacy analyses compared the treatment groups with respect to the change from baseline in the mean number of hot flashes per day to the week 12 (cycle 3).

Reviewer’s Comment

In this Phase 4 study severity was not reviewed as a primary efficacy variable. This is clearly inconsistent with the Division’s long time recommendation of a statistically significant mean difference in the reduction of frequency and severity of moderate to severe hot flushes.

The following table from the original primary reviewer shows the results of the primary efficacy analysis:

Table 18: Primary Efficacy Analysis Study 1003A

Treatment group of E ₂	Baseline	Cycle 1	Cycle 2	Cycle 3	Last Cycle
	N LS	N LS	N LS	N LS	N LS
	Means (SE)	Means (SE)	Means (SE)	Means (SE)	Means (SE)
0.0375mg/day	41 (9.83 (1.13)	41 -3.38 (0.69)	39 -6.47 (0.69)	39 -6.77 (0.71)*	45 -6.11 (0.68)
0.05mg/day	44 12.92 1.09	43 -3.55 (0.68)	43 -5.74 (0.68)	43 -6.75 (0.66)*	49 -6.55 (0.28)
0.075mg/day	40 12.64 (1.16)	39 -5.62 (0.72)*	38 -8.15 (0.69)*	37 -8.35 (0.73)*	46 -8.11 (0.68)
0.1mg/day	40 12.22 (1.14)	39 -7.95 (0.69)*	36 -8.63 (0.72)*	33 -9.28 (0.78)*	42 -9.19 (0.75)
Placebo	44 10.76 (1.14)	43 -1.94 (0.69)	39 -4.32 (0.69)	38 -3.70 (0.71)	49 -2.82 (0.66)
Overall p-value	0.25	0.0001	0.0001	0.0001	0.0001

*Significantly different from placebo

Note the 0.75 and 0.1 dosages are statistically different at all three treatment cycles while the 0.5 and 0.0375 dosages are only significant in cycle 3.

6.1.5 Analysis of Secondary Endpoints(s)

The main secondary analysis was the severity of hot flashes; the following table shows the reduction in the severity of hot flushes/flashes:

Reviewer’s Comment

Although the sponsor states that severity is a secondary efficacy analyses in this study the efficacy of estrogen products have always been based on a statistically significant reduction in both frequency and severity of hot flashes.

Table 19: Mean reduction in the severity of hot flushes/flashes:

Treatment group of E ₂	Baseline		Cycle 1		Cycle 2		Cycle 3		Last Cycle	
	N	LS	N	LS	N	LS	N	LS	N	LS
	Means (SE)		Means (SE)		Means (SE)		Means (SE)		Means (SE)	
0.0375mg/day	41	4.91	41	-1.25 (0.23)	39	-2.39* (0.3)	39	-2.40 (0.33)	45	-2.27* (0.29)
0.05mg/day	44	5.55 (0.28)	43	-1.25 (0.23)	43	-2.34 (0.28)	43	-2.60* (0.30)	49	-2.53* (0.29)
0.075mg/day	40	5.30 (0.30)	39	-2.19* (0.24)	38	-3.46* (0.33)	37	-3.40* (0.33)	46	-3.47* (0.29)
0.1mg/day	40	5.06 (0.31)	39	-2.77* (0.25)	36	-3.58* (0.31)	33	-3.70* (0.36)	42	-3.56* (0.32)
Placebo	44	5.04 (0.29)	43	-0.74 (0.23)	39	-1.39 (0.33)	38	-1.39 (0.33)	49	-1.09 (0.28)
Overall p-value	0.54		0.0001		0.0001		0.0001		0.0001	

- *Significantly different from placebo
- Note the 0.75 and 0.1 doses are statistically different at all three treatments cycles. Only the second cycle is the 0.0375 mg dose statistically significance different from placebo; only in the third cycle is the 0.05 dose statistically significantly different from placebo.

Study 1003B

The purpose of study 1003B was to evaluate the safety and efficacy of two dosages of the Noven EDTS 0.0375 mg/day and 0.1 mg/day. This study enrolled 120 subjects who met all protocol requirements. This was a multi-center, double-blind, randomized, placebo controlled trial involving seven centers

All inclusion and exclusion criteria were the same as in study 1003A and the clinical trial was run in the same manner.

One hundred twenty-two (122) subjects were randomized at the seven US centers. There were 42 subjects randomized to estradiol 0.0375mg/day, 39 subjects randomized to estradiol 0.1mg/day and 41 subjects randomized to placebo. Of this total, 110 were eligible for efficacy analysis, 38 receiving 0.0375 36 receiving 0.1mg and 36 received placebo (two subject were lost to follow-up, one subject was not eligible as data was not provided due to an adverse event, and nine subjects had protocol violations). Importantly, there was one week of each cycle where no patch was worn (3 weeks on –

one week off regimen); therefore subjects were exposed to nine weeks of active treatment. Of note, the sponsor enrolled subjects with mild symptoms that were later excluded from the final efficacy analyses. The age range was 31.2 years to 65 years of age. The mean age per group was 48.5 with the 0.1 group being statistically older by four years (not significant). Of the 110 evaluable subjects, 97 were white, 10 black, and three Hispanic. Seventy-three percent (72.7%) experienced a natural menopause.

Reviewer’s Comment

A per protocol evaluation was performed instead of a MITT.

The primary efficacy variable in this study was the change in the number of hot flashes from baseline. The mean number of hot flashes recorded at weeks 2 and 3 for the placebo run-in period was used as baseline. Mean number of hot flashes for the double blind period was the average number of hot flashes during the second and third weeks each cycle. The primary time point was the third active treatment period.

A total of 122 subject were randomized, 42 to the estradiol 0.0375mg/day, 39 to estradiol 0.1 mg/day and 41 to placebo. Of the 110 evaluable subjects, 38 received 0.0375mg/day, 36 received 0.1mg/day and 36 received placebo. Reasons for exclusion were loss to follow-up (12), adverse event (1), protocol violations (9).

Efficacy results are show in the following table:

The following table from the MOR shows the Mean Reduction in Number of Hot Flashes—Study 1003B

Table 20: the Mean Reduction in Number of Hot Flashes—Study 1003B

Treatment	Baseline	Cycles					
		1		2		3	
		OBS	Change	OBS	Change	OBS	Change
0.0375mg/day	10.9	5.5	-5.4*	3.7	-7.2*	2.9	-8.0
0.1mg/day	11.5	4.2	-7.4*	2.3	-9.2*	1.8	-9.4*
Placebo	10.2	9.2	-1.1	8.0	-2.2	7.4	-2.7

Obs= Observed

*Statistically significant from placebo

Differences between two active groups is not significant

Note, at each active treatment cycle, the active treatments were significantly different form placebo. However, the differences between the two active groups were not statistically significant.

Severity of hot flashes was the main secondary efficacy parameter. There was a statistically significant difference (p < 0.001) between treatment groups for each active cycle with both active treatments have a statistically significant reduction in the severity of hot flashes compared to placebo. Differences between the two active groups were

only significant at the first treatment cycle with the 0.1mg/day group demonstrating greater reduction in severity.

In study 1003B there was a statistically significant difference reduction in the severity of sweating ($p < 0.001$) at each active treatment cycle.

Reviewer's Overall Comment on Efficacy of Studies 1003A and 1003B

Study 1003A was the primary study to assess efficacy of Vivelle. Study 1003A did not demonstrate efficacy at the 0.0375mg/day and 0.050 mg/day doses. Study 1003B also did not support efficacy of the 0.0375 mg/day dose (the 0.050 mg/day dose was not studied). Additional re analyses in the review cycle did not support the efficacy of the 0.0375 mg/day dose. The sponsor conducted a bioequivalence study between the Noven 0.050mg/day patch and the approved Estraderm patch[®] 0.05mg/day patch. Bioequivalence was demonstrated. This reviewer recommended non-approval of both the 0.0375 and 0.050 mg/day because of failure of the clinical trial data to demonstrate a statistically significant improvement at the end of cycle 1 (Week 4) *and* at the end of cycle 3 (Week 12). From my standpoint, the findings from a pharmacokinetic Phase 1 study should not be accepted as evidence of efficacy when efficacy is not demonstrated in a clinical trial. However, the Division Director agreed with the Sponsor that the BE data could support approval of the 0.050 mg/day dose and that the 0.0375 dose would be approved with restrictive language "stating that women taking the 0.035 dosage may experience a delay in the onset of efficacy." Approval also required a Phase 4 commitment to provide clinical data supporting removing the restrictive language on the delay to onset of efficacy. Efficacy of the 0.0375 mg/day dose was subsequently demonstrated in the Phase 4 study.

Supplement021- Protocol 036

Protocol 036 (submitted April 30, 1999) was a randomized, double-blind, parallel group, 12-week, multicenter study comparing Vivelle 0.0375 to placebo for the treatment of moderate to severe postmenopausal hot flashes. Approximately 250 subjects (125 per treatment group) were enrolled in order to obtain a total of 228 evaluable subjects per treatment group.

Inclusion and exclusion criteria were consistent with studies 1003A and 1003B with the exception of a shorter run-in period of 10 days vs. 14 days in the other studies.

Study Procedures were consistent with studies 1003A and 1003B. The patch was applied twice a week (on the same day of the week (e.g. Monday and Thursday of each week) to a clean dry, unbroken area of the skin on the buttock that was not oily, damaged or irritated. The waistline was to be avoided since tight clothing could rub off the system.

Sample size for this trial was based on the previous trials and was derived from the standard deviation (SD) of the number of hot flushes per day during Cycle 1. It was expected that the SD of the number of hot flushes per day during Cycle 1 would be 4.8 flushes per day, and the SD of the severity of hot flushes would be 1.39. In order to detect a difference of 0.52 in overall severity of hot flushes per day during cycle 1 between placebo and Vivelle 0.0375 with a significance level of 0.05 (two-sided) and power of 80% a total of 114 evaluable patients per treatment group was required. This sample size would be sufficient to detect a mean difference (ETDS vs. placebo) of 2.0 hot flushes per day.

Results

Approximately 259 subjects were randomized into the double blind treatment phase of the trial. Two-hundred forty-six (246) completed the trial (128 Vivelle, 118 Placebo).

The following table from the MOR shows the distribution of subjects by treatment group:

Table 21: Distribution of subjects by treatment group (all randomized subjects)

Number of Subjects	Vivelle 0.0375 mg/day	Placebo	Total
Randomized	130	129	259
Treated (at least one application)	130	127 ¹	257
Completed	128	118	246
Discontinued prematurely ²			
Total	2	11	13
For Adverse Event	1	3	4
For unsatisfactory therapeutic effect	0	2	2
For any reason	1	6	7
Efficacy Analyses			
Acceptable Subjects	125	117	242
Intent-to-treat	130	127	257
In Safety Analyses			
Adverse experience evaluation	130	127	257
Safety Laboratory Evaluation	129	127	256

1 Two subjects in the placebo group (MO465U/220 and MO458D/380) did not provide any post-baseline data and are lost to follow-up. These two subjects were excluded from both the safety and efficacy analyses.

2 Overall, 13 (5%) subjects discontinued from the study prematurely. Of this total, 3 (one in the 0.0375mg group and two in the placebo group) were lost to follow-up. The seven subjects in the "for any reason group" appeared to have valid reasons for discontinuation.

Demographics

The mean age in study was approximately 50.4 years of age for both treatment groups. Approximately 216 (83.4%) were White, 33 (12.7%) were African American, and 10 (3.8%) were "Other." The treatment groups were comparable with a mean weight of

160.6 lbs. Menopausal status criteria included the following: >12 months of amenorrhea 53 (20.2%), 6-12 months 7 (2.7%), hysterectomized subjects 49 (18.9%), post bilateral oophorectomy 149 (57.5%), and missing data 1 (4%). In regards to smoking status, 63 (24.3% were smokers and 196 (75.7%) were non-smokers. Mean baseline number of hot flushes was 11.41 in the Vivelle group and 11.59 in the placebo group; mean severity of hot flushes (0-4 scale) was 2.53 in the Vivelle group and 2.55 in the placebo group.

The following table from the MOR shows the Change from baseline in the mean number of hot flushes for per 24 hours in the last two weeks of cycle 1 (ITT) population Protocol 036

Table 22: Change from Baseline in the Mean Number of Hot Flushes for per 24 hours in the Last Two Weeks of Cycle 1 (ITT) population

Cycle 1	Vivelle 0.0375mg/day				Vivelle/Placebo		
	Baseline	N	Mean (SD)	N	Mean	Difference	P-Value
		130	11.9 (5.4)	126	11.7 (5.5)		
	Post-treatment	130	4.0 (4.2)	126	6.8 (5.6)		
	Difference	130	-7.9 (5.6)	126	-4.9 (4.7)	-3.0	<0.001*

*Significance is assessed when $p < 0.05$ (two-sided)

Note there is a difference of three hot flushes per day in the ITT population which is statistically significant at the $p < 0.001$ (two-sided)

Table 23: Change from baseline in the mean number of hot flushes for per 24 hours for Cycles 2 and 3

Cycle	Vivelle 0.0375mg/day				Vivelle/Placebo		
		N	Mean (SD)	N	Mean (SD)	Difference	P-Value
2	Baseline	125	11.5	120	11.3		
	Post-treatment	128	2.9	120	5.9		
	Difference	128	-8.6 (0.35)	120	-5.39	-3.21	<0.001*
3	Baseline	124	11.5 (5.2)	117	11.3 (4.8)		
	Post Treatment	124	2.3 (3.6)	117	5.6 (4.9)		
	Difference	124	-9.24	117	-5.65	-3.59	<0.00*

*Significance is assessed when $p < 0.05$ (two-sided)

Note Vivelle is statistically better at cycles 2 and 3 with differences of -3.31 and -3.59 at the end of cycles 2 and 3. This supports the previous study (study 1003A) showing efficacy after cycle 1(week 6).

Note: Cycles 1, 2, and 3 correspond to Weeks 4, 8 and 12.

The following table from the MOR shows the change from baseline in mean severity of hot flushes in Cycles 2 and 3.

Table 24: Change from Baseline in Mean Severity of Hot Flushes in Cycles 2 and 3 (ITT subjects)

Cycle		Vivelle 0.0375mg/day			Vivelle/Placebo		
		N	Mean (SD)	N	Mean (SD)	Difference	P-Value
2	Baseline	129	2.5 (0.4)	120	2.6 (0.4)		
	Post-treatment	129	1.0	120	1.7 (0.8)		
	Difference	129	-1.55 (0.07)	120	-0.83 (0.08)	-0.71	<0.001*
3	Baseline	128	2.5 (0.4)	118	2.5 (0.4)		
	Post Treatment	128	0.8 (0.9)	118	1.6 (0.9)		
	Difference	128	-1.77 (0.08)	118	-0.92 (0.08)	-0.85	<0.001*

Note Vivelle is statistically significant better than placebo in cycles 2 and 3 in relieving the overall severity of hot flushes. This again supports data from study 1003A in the original review.

Note: Cycles 2 and 3 correspond to Weeks 8 and 12.

Reviewer's Overall Comment

Tables 22 to 24 summarize the data from Protocol 036. In the original review efficacy was not demonstrated for the 0.0375mg/day dose; the 0.0375mg/day dose was approved with restricted labeling that noted a delay in relief of symptoms. Protocol 036 demonstrated efficacy for the 0.0375mg/day dose and the restrictive labeling was removed from Vivelle.

6.1.6 Other Endpoints

There were no significant differences noted in the daily severity of headache, insomnia, urge to urinate, or in the severity of vaginal discomfort in either study 1003A and 1003B.

6.1.7 Subpopulations

No subpopulations were study in this NDA.

7 Review of Safety (this section will present a historical summary of previously reviewed data)

Safety Summary

Safety data from Study 1003A and Study 1003B and Protocol 036 will be summarized separately.

Study 1003A

There were 234 subjects in the safety database. One hundred seventy-four (174) experienced some type of adverse event. There were no statistically significant differences in the number of subjects reporting adverse experiences ($p = 0.277$; chi-square test) across treatment groups. Overall, a total of 34/185 (18%) of subjects in all active treatment groups experienced a severe adverse event compared to 11/49 (22%) in the placebo groups. One subject the 0.075mg/day group and one in the 0.1mg/day group experienced a SAE; two subjects in the placebo group experienced a SAE, but neither was considered drug related. One subject (0.1mg/day group) was classified as possibly related the drug; that subject had transient visual loss and visual change and was removed from the study after only four days of treatment.

There were no deaths in this study. There were four subjects with SAEs, three probably were unrelated and one possibly related. The subject with possible relationship to study drug used the 0.1mg/day dose with ETDS remaining on for four days and experienced transient visual loss and visual changes; she was discontinued from the study. The other three subjects experienced the following events: a concussion and fracture of the left arm (placebo group), severe abdominal pain with a cholecystectomy (0.1mg/day group), and abdominal pain, vomiting and diarrhea (placebo).

Adverse events by number and percentage of subjects reporting an AE in each treatment group were recorded across all dosage treatment groups by body system. Headache was reported 21(43.7%) in the treatment groups vs. 22 (44.9%) for placebo; pain was reported in 22 (11.9%) in the treatment groups vs. 2 (4.1%) in the placebo group; flu-like syndrome was reported in 16 (8.6%) of the treatment group vs. 7 (14.3%) in the placebo group; rhinitis was reported in 19 (10.3%) of the treatment groups vs. 6 (12.2%) in the placebo group; breast pain was reported in 10 (5.4%) in the treatment groups vs. 0% in the placebo group; skin and appendages, 7 (3.8%) reported rash, 1 (0.5%) reported urticaria, 3 (1.6%) reported acne, and 2 (1.1%) reported pruritis in the treatment groups vs. 2 (4.1%) rash, 1 (2.0%) urticaria, and 0% was reported for acne or pruritis in the placebo group, respectively.

Endometrial biopsies were collected at three centers during the study. Three subjects (1.6%), one in the 0.050mg/day group, and two in the 0.1mg/day group had either mild or simple hyperplasia. Although no atypical hyperplasia was reported, this non-continuous, short term treatment produced hyperplastic changes. The clinical reviewer

recommended that endometrial sampling or concomitant use of a progestin should be considered.

Study1003B

Subjects were required to apply the patch every 3.5 days for three week of each four week cycle. There was one week of each cycle when no patch was worn. Subjects were exposed to nine weeks of active drug. Total adverse events are 720 (509 active treatments, 211 placebo). Of the 81 subjects receiving active drug, 63 (78%) reported an adverse event, irrespective of causality compared with 30/41 (73%) in the placebo group.

Review of drug related AEs showed that in the 0.0375mg/day group, the 0.1mg/day group and the placebo groups, eight, five and four subjects had drug related AEs, respectively. One subject in the placebo group withdrew from the study because of continued coughing.

The most commonly reported adverse events were: headache (21) flu (20), rhinitis (17), pain (13), back pain (12), nausea (9), rash (9) erythema (8), dyspepsia, edema, myalgia, dizziness and pruritis (7 each).

In most cases, it appears that skin problems were classified as mild. Approximately 80% had either no irritation or slight irritation with the 0.1mg dose. Approximately 84% to 95% had no pruritis at any visit, while 10% had slight irritation. The 0.1mg/day group differed at Visit 7 (last visit), 78% had no irritation and 19% had slight irritation. Vesicles were seen in very few subjects, and a few subjects showed papules. At Visit 7, two subjects (5%) in the 0.1mg/day group had slight papules compared to no papules with any of the other three EDTS groups.

Protocol 036

There were no deaths. Overall, 42/130 (32.3% reported at least one drug related AE in the Vivelle 0.0375mg/day group compared to 19/127 (15.5%) in the placebo group. Two subjects in the Vivelle 0.035mg/day group had a serious AE (two cases of simple hyperplasia).

The most frequent AEs reported at least once were viral infection (0.0375mg/day group 10%, placebo 13.4%, breast pain 0.0375mg/day group 10%, placebo 0.8%), sinusitis (0.0375mg/day 7.7% placebo 8.7%), headache (0.0375mg/day group 6.2%, placebo 7.1%), insomnia (0.0375mg/day group 2.3%, placebo 7.1%, genital disorder, i.e., vaginal yeast infection (0.0375mg/day group 6.2%, placebo 1.6%), and upper respiratory tract infection 0.0375mg/day group 6.9%, placebo 4.7%).

Reviewer's Comment

In Study 1003A, Study 1003b and Protocol 036 similar adverse drug reaction profiles are noted; there were few serious adverse events with the exception of

the two simple hyperplasia cases. Irritation was noted to occur with increasing patch size. Safety data was consistent with the original studies 1003A and 1003b.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Since this is a pharmacokinetic submission this section is not applicable.

7.1.2 Categorization of Adverse Events

Since this is a pharmacokinetic submission this section is not applicable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Since this is a pharmacokinetic submission this section is not applicable.

7.2 Adequacy of Safety Assessments

Since this is a pharmacokinetic submission this section is not applicable.

7.3 Major Safety Results

Since this is a pharmacokinetic submission this section is not applicable.

8 Postmarket Experience

No additional postmarket experience is deemed necessary

8.1 Literature Review/References

None

8.2 Labeling Recommendations

Draft labeling has been sent to the sponsor

8.3 Advisory Committee Meeting

No Advisory committee is recommended.

9 Appendices

Sponsor table 9-1: Schedule of Activities and Assessments

Table 25: Schedule of Activities and Assessments (Study N26-004)

Study Day	Screening -23 to -2	Treatment Period 1										Washout 7-20	Treatment Period 2								End of Study or Early Termination 27 Sun
		Admission -1	Baseline 0	1	2	3	4	4	5	6	Admission 21		22	23	24	25	25	26	27		
		1900 hrs Sun	-24 Mon	0 Tue	24 Wed	48 Thurs	72 Fri	84 Fri	96 Sat	120 Sun	1900 hrs Mon		0 Tue	24 Wed	48 Thurs	72 Fri	84 Fri	96 Sat	120 Sun		
Clinic Admission	X											X									
Inspect Subject's Belongings	X											X									
Breakfast 0700 hours		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X			
Lunch 1230 hours		X	X	X	X	X	X	X	X				X	X	X	X	X				
Dinner 1800 hours		X	X	X	X	X	X	X	X				X	X	X	X	X				
Snack 2200 hours		X	X	X	X	X	X	X	X			X	X	X	X	X	X				
Informed Consent	X																				
Assign Screening Number	X																				
Inclusion/Exclusion Criteria	X																				
Medical History	X																				
Physical Examination	X																	X			
Gynecological Examination (including breast and pelvic exam)	X																				
Pap Smear	X																				
Mammogram	X																				
Vaginal ultrasound	X																				
Height and Weight	X																	X (weight only)			

Clinical Review
 Phill H. Price, M.D.
 NDA 203752
 Minivelle (estradiol transdermal delivery system)

Study Day	Screening -23 to -2	Treatment Period 1										Washout 7-20	Treatment Period 2								End of Study or Early Termination 27				
		Admission -1	Baseline 0	1	2	3	4	4	5	6	Admission 21		22	23	24	25	25	26	27						
Inpatient Visit		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Scheduled Hour		1900 hrs	-24	0	24	48	72	84	96	120		1900 hrs	0	24	48	72	84	96	120						
Day of Week		Sun	Mon	Tue	Wed	Thurs	Fri	Fri	Sat	Sun		Mon	Tue	Wed	Thurs	Fri	Fri	Sat	Sun					Sun	
Vital Signs	X			X									X											X	
12-lead ECG	X																							X	
Clinical Laboratory	X																							X	
Urinalysis	X																							X	
Estradiol, LH and FSH Levels	X																								
Urine Drug Screen	X	X										X													
Hepatitis B and C and HIV	X																								
Urine Pregnancy Test (all females less than 2 years postmenopausal)		X										X													
Breathalyzer	X	X										X													
Randomization				X																					
Visual inspection of skin at application site				X									X												
Patch Application				X									X												
Patch Removal									X														X		
Patch Adhesion				X	X	X	X	X					X	X	X	X	X					X	X	X	
Irritation Assessment								X	X	X												X	X	X	
Discomfort Assessment				X	X	X	X	X					X	X	X	X	X								
Adhesive Residue								X														X			

Study Day	Screening -23 to -2	Treatment Period 1										Washout 7-20	Treatment Period 2								End of Study or Early Termination 27				
		Admission -1	Baseline 0	1	2	3	4	4	5	6	Admission 21		22	23	24	25	25	26	27						
Inpatient Visit		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Scheduled Hour		1900 hrs	-24	0	24	48	72	84	96	120		1900 hrs	0	24	48	72	84	96	120						
Day of Week		Sun	Mon	Tue	Wed	Thurs	Fri	Fri	Sat	Sun		Mon	Tue	Wed	Thurs	Fri	Fri	Sat	Sun					Sun	
PK Blood Sample			X	X	X	X	X	X	X	X			X	X	X	X	X	X	X						
Discharge from Clinic										X														X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study N28-005 Sponsor's Table 9-1

Table 26: Schedule of Activities and Assessments (Study N28-005)

Study Procedures	Screening	Treatment Periods 1, 2, and 3			End of Study (Day 48 or Early Termination)	Follow-up (7-10 days following discharge)
		Day -1, Day 21, and Day 42	Day 0 - Day 1	Days 1-6, Days 22- 27, and Days 43-48		
Informed Consent	X					
Medical History	X					
Physical Examination (complete)	X				X	X
Vitals Signs	X	X		X	X	X
Chemistry ¹	X				X	X
Hematology ¹	X				X	X
Urinalysis	X				X	X
Urine Drug Screen and Alcohol	X	X ²				
Urine Pregnancy Test	X	X				
Hepatitis B and C antigen	X					
HIV Antibody	X					
PAP Smear ³	X					
Mammogram ⁴	X					
Transvaginal Ultrasound ³	X					
Estradiol Level	X					
FSH Level	X					
LH Level	X					
12-lead ECG	X				X	X
Check Belongings		X				
Physical Examination (interim)		X				
System Application ⁴				X		
Blood Sampling			X	X		
Adherence & Discomfort Evaluation				X		
System Removal				X		
Skin Irritation				X		
Adhesive Residue Evaluation				X		
AEs & Concomitant Medications		X		X	X	X

¹Following fasting for at least 8 hours, ²Or a breathalyzer test, ³If one was not done within 3 months of study initiation; ⁴If one was not done within 9 months of study initiation.
⁵On all subjects with an intact uterus

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/s/

PHILL H PRICE
10/04/2012

SHELLEY R SLAUGHTER
10/05/2012

I concur with Dr. Price's conclusions and his recommendation that NDA 203,752 receive an Approval.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	are known to occur with the drugs in the class to which the new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths in studies
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Sponsor request Pediatric waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			pK datasets for 2 studies
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	N/A for this submission
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	N/A for this submission
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___X___

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No review issues for clinical review team

Phill H. Price, M.D.	February 14, 2012
_____ Reviewing Medical Officer	_____ Date

_____ Clinical Team Leader	_____ Date
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/s/

PHILL H PRICE
02/23/2012