CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 22-014
Submission Number	000
Submission Code	N
Letter Date	September 28, 2006
Stamp Date	September 29, 2006
PDUFA Goal Date	July 27, 2007
Reviewer Name	Phill H. Price, M.D.
Review Completion Date	July 26, 2007
Established Name	Estradiol
(Proposed) Trade Name	Evamist™ (estradiol transdermal spray
Therapeutic Class	Estrogen
Applicant	Vivus, Inc.
Priority Designation	S
Formulation	Estradiol 1.53mg
Dosing Regimen	1, 2 or 3 sprays daily
Indication	Treatment of Moderate to Severe Vasomotor Symptoms
Intended Population	Perimenopausal and Postmenopausal women

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1 EXECUTIVE SUMMARY

Approval of estradiol 1.53mg in the form of 1, 2 and 3 sprays is recommended for the treatment of moderate to severe vasomotor symptoms. The efficacy of Evamist™ (estradiol transdermal spray) was demonstrated in pivotal trial EST-01.

1.1 Recommendation on Regulatory Action

Sufficient evidence is provided to conclude that Evamist™ 1.53mg, 1, 2, and 3 spray dosages, provides relief in the treatment of frequency and severity of moderate to severe vasomotor symptoms that begins in the fourth week of treatment and is maintained through treatment week 12. This reviewer notes that in study EST-01 there appears to be little clinical difference between the 2-spray dose and the 3-spray dose (supported by pharmacokinetic data showing little difference in the C_{max} and C_{aver} between 2-spray and 3-spray dosages at day 14). Additional data supplied by the sponsor support the concept that during the entire course of treatment the 3-spray dose supplies higher serum levels of estradiol than the 2-spray over days 2-13 of treatment for both estradiol and estrone in study EST-01. Further support of a clinical difference between the 3-spray and 2-spray doses is shown in study EST-01 where subjects who had a positive response to treatment had higher measured serum levels of estradiol than in subjects who did not respond to treatment at treatment weeks 4 and 12. Therefore, this reviewer recommends all three dosages for approval. Safety of this product is not a major concern; serious and common adverse events are consistent with other transdermal products used to treat moderate to severe vasomotor symptoms.

1.2 Recommendation on Postmarketing Actions

Based upon pharmacokinetic data presented in this submission, this reviewer recommends that the sponsor study the thigh as an alternative site of application.

1.2.1 Risk Management Activity

No additional risk management is deemed necessary. The one spray dosage appears to offer the lowest effective dose of this product.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitment is being sought. This product has an acceptable safety profile at all dosages studied.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor, Acrux, has submitted study EST-01to support approval of Evamist™. Study EST-01 is a Phase 3, 12-week, randomized, double-blind, multi-center, placebo-controlled trial to evaluate the safety and efficacy of estradiol transdermal spray (1, 2, or 3 sprays daily) for treatment of vasomotor symptoms in postmenopausal women. The estradiol is delivered by a new dosing applicator. The Agency recommends at least one adequate and well-controlled trial that is sufficiently powered to support approval of a transdermal estradiol product in the US.

1.3.2 Efficacy

The sponsor studied Evamist ™ using containing 1.53 mg of extradiol delivered in a 1, 2-spray and 3-90µL sprays. For the primary efficacy variable of frequency, all three dosages were demonstrated to be effective in the reduction of the frequency of hot flushes at weeks 4 and 12. For the primary efficacy variable of severity the 1-spray dose demonstrated delayed effectiveness *at week 4(p = 0.057) and was effective from weeks 5 through week 12;* the 3-spray and 2-spray dosages demonstrated effectiveness for severity at weeks 4 and 12.

1.3.3 Safety

The safety of Evamist™ is supported by study (EST-01). The criteria used to assess the safety of Evamist™ were adverse events (AEs), vital signs, physical examinations, transvaginal ultrasound, mammogram and clinical laboratory tests. Approximately 458 subjects were randomized into treatment, 454 received at least one dose of the test material and were analyzed for safety in the intent-to-treat population (ITT).

The most frequent reported AEs were headache, breast tenderness, metrorrhagia, nausea, back pain, nasopharynitis and arthralgia. No dose proportionality was noted across treatment groups. There were no thromboembolic events in any treatment group.

No new safety concerns were observed in study EST-01. Adverse events coding using the Medical Dictionary for Regulatory Activities (MedDRA) was employed.

1.3.4 Dosing Regimen and Administration

The sponsor studied 1.53mg estradiol delivered in a 90µL spray at 1-spray, 2-sprays and 3-sprays. Evamist™ should be initiated with one spray per day and dosage adjustment should be guided by the subject's clinical response. One, two or three sprays should be applied daily to the *inner surface of the arm between the elbow and wrist* and allowed to dry. b(4)

1.3.5 Drug-Drug Interactions

Drug interactions are well defined for the class of estrogen products. No special studies were conducted with Evamist™ in regards to drug interactions.

1.3.6 Special Populations

No special populations were studied with this product.

2 INTRODUCTION AND BACKGROUND

Vasomotor symptoms (hot flushes and sweating) associated with the menopause are generally reported to be the most frequent reason for women to seek hormone therapy (HT). Although estradiol therapy alleviates many postmenopausal symptoms, the use of therapeutic dosages of estrogen-only HT in women with an intact uterus is associated with an increased risk of endometrial hyperplasia and adenocarcinoma of the estrogen. The Agency recommends the lowest effective dose for the shortest period of time be used to treat vasomotor symptoms.

2.1 Product Information

Evamist™ (estradiol transdermal spray) contains 1.53mg of estradiol in a solution of alcohol and octisalate. The metered-dose pump delivers fifty–six 90μL sprays.

- Evamist™ — Estradiol (1.53mg) delivering 90 μL of estradiol
- Established name: — Evamist™ (estradiol transdermal spray)
- Chemical name: — Estradiol USP (estra-1,3,5, (10)-triene-3, 17β
- Pharmacological class: — Estrogen
- Proposed Indication: — Treatment of moderate to severe vasomotor symptoms associated with menopause

2.2 Currently Available Treatment for Indications

There are several estradiol transdermal estradiol patches and gels currently approved and distributed by a number of manufacturers to treat vasomotor symptoms. These transdermal preparations provide multiple dosages.

2.3 Availability of Proposed Active Ingredient in the United States

Estradiol has been widely available in the US market for over 50 years. Estradiol has been used as the mainstay for the treatment of vasomotor symptoms since the 1940's. In the early 1990's the use of a concomitant progestin became standard of care in the treatment of vasomotor symptoms in an effort to reduce the incidence of endometrial hyperplasia (as well as atypical hyperplasia), the precursor to development of endometrial cancer.

2.4 Important Issues with Pharmacologically Related Products

Since publication of the results of the Women's Health Initiative (WHI) in 2002, manufacturers of products for hormone therapy have been encouraged to produce lower dose products in order to provide a greater risk/benefit ratio. The WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during the 5.2 years of treatment with oral conjugated estrogen (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogen plus medroxyprogesterone acetate relative to placebo.

2.5 Presubmission Regulatory Activity

Regulatory guidance and advice was sought and obtained on a number of occasions between the sponsor and the Agency. This guidance was primarily related to the design and statistical analysis of the Phase 3 trial.

The following are significant regulatory issues that were discussed between the Agency and the sponsor:

A special protocol assessment (SPA) for EST-01 was submitted by Vivus on July 15: the Agency responded to the initial request for the SPA on September 2, 2004. Vivus submitted a response to the Agency on April 25, 2005; the Agency provided comments on July 21, 2005. The following issues were reviewed and resolved:

a The Agency agreed that the overall protocol design for the Phase 3 VMS trial was adequate and that a single Phase 3 trial, as opposed to two separate studies, was acceptable.

b. Vivus originally suggested using a 10-point severity scale for VMS in the daily dairy card; the Agency recommended deleting this scale and using clinical definitions of mild, moderate, and severe symptoms to describe the severity of VMS; Vivus accepted the Agency's recommendation.

c. The Agency suggested, and the sponsor agreed, that the sample size should be increased to approximately 74 subjects per treatment group to account for potential dropouts.

d. Dose selection followed the January 2003 Draft Guidance for Industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation". This document is subsequently referred to in this review as the 2003 Draft HT Guidance.

e. The sponsor added a third dosing group (3-spray) to the original protocol to ensure that adequate systemic exposure was achieved.

f. The Agency agreed to the inclusion/exclusion criteria recommended by the sponsor for Phase 3.

g. The Agency recommended, and the sponsor agreed, that the primary endpoints were the mean change in frequency of moderate to severe VMS from baseline to week 4 and to week 12 and the mean change in severity of moderate to severe VMS from baseline to week 4 and to week 12. Change from baseline in frequency and severity to moderate to severe hot flushes at week 8 was added to the protocol as a secondary endpoint.

h. The sponsor agreed to efficacy analyses for the following age subgroups: less than 50 years of age, 50-59 years of age, and greater than 59 years of age were included in the protocol and the analysis plan.

i An agreement was made in regards to the handing of missing data; all cases of an incomplete diary primary endpoint would be handled by imputation with the last observation carried forward for the ITT/safety and modified ITT populations.

j. The Agency sought clarification of the statistical adjustment procedure being applied for the control of Type I error relating to the testing of the three dose arms.

The SAP was submitted on November 10, 2005; the initial response from the Agency was dated January 20, 2006. A revised SAP was submitted on February 9, 2006 and a teleconference was held on April 13; agreement was reached concerning the Agency's acceptance of the SAP. The final SAP was submitted on April 26, before the database lock and unblinding of any data occurred.

Recommendation on the NDA content and filing strategy were proposed by Vivus in a correspondence on November 10, 2005 and agreed to by the Agency on January 20, 2006.

A pre-NDA CMC meeting was held on April 26, 2006 and agreements were made between Vivus and the Agency.

A pre-NDA clinical meeting was held on June 28, 2006 and agreements were made between the Agency and Vivus. Most important of these agreements was the Agency's acceptance of the plans for summaries of Biopharmaceutics, Clinical Pharmacology, Clinical Efficacy and Clinical Safety in the submission; the fact that Evamist™ meets the requirements for exclusion from pediatric study requirements; the Agency's request for subgroup analyzes on BMI; additional secondary supportive information on responder analyzes at 75%.

2.6 Other Relevant Background Information

No additional relevant information was submitted with this NDA.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

There have been no unusual nonclinical data, chemistry or manufacturing controls (CMC) microbiology or pharmacology/toxicology issues that evolved during the review of this supplement.

3.1 CMC (and Product Microbiology, if Applicable)

Estradiol is a well-established active pharmaceutical ingredient with compendial monographs included in both the United States and European Pharmacopeias. Drug substance is obtained from a GMP manufacturer, [redacted], and information on [redacted] estradiol is provided in DMF [redacted]

b(4)

Octisalate was chosen as the penetration enhancer based on its ability to efficiently enhance estradiol penetration in a pilot human study. The ratio of — for estradiol:octisalate was chosen from in-vitro skin diffusion studies. The amount of estradiol and octisalate contained in the final formulation was determined ——— b(4)
——— Based on these factors, the final formulation contained 1.7% w/v estradiol and ———octisalate. Octisalate is highly lipophilic, is practically insoluble in water, and is miscible with ethanol.

Alcohol USP, ——— was chosen as the volatile solvent in the estradiol transdermal spray formulation. Ethanol — dissolves the estradiol and octisalate, can be sprayed via a metered-dose pump, and evaporates quickly once applied to the skin. Ethanol has been used as a penetration enhancer in transdermal and topical products. *Ethanol helps solvate the stratum, depositing the estradiol and octisalate in the stratum corneum to create a depot.* One clinical study (EST-06) has shown that 1 hour after the formulation has been applied the drug cannot be washed off the surface of the skin. b(4)

3.2 Animal Pharmacology/Toxicology

There were no new major pharmacology/toxicology issues identified. One minor issue related to the percentage of octisalate in the formulation. In sunscreens, the maximum amount of octisalate is 5%. The formulation with Evamist™ contains —— octisalate which is outside the OTC monograph. After review of the literature it was determined by the pharmacology/toxicology review team that the — octisalate would pose no additional health hazard. b(4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The sponsor presented an integrated summary of safety and efficacy for pivotal study EST-01 that contains safety and efficacy supporting the effectiveness of 3 dosages (1-spray, 2-sprays, and 3-sprays) of Evamist™. The sponsor presented two Pharmacokinetic studies (EST-02, EST-06) that were used to evaluate factors that could affect estradiol absorption. In addition, in summary form, the sponsor submitted 5 summaries of Phase 1 studies conducted by Acrux Ltd. These 5 studies (FHRT0001, FHRT0002, FHRT0005, FHRT09 and FHRT06) investigated various proportions of estradiol and two different penetration enhancers in order to identify an appropriate formulation that would result in therapeutic levels of systemic estradiol when delivered by transdermal spray. These studies demonstrated that a formulation containing 1.7% 17β estradiol and — octisalate was able to deliver estradiol into the systemic circulation in amounts similar to a currently approved transdermal estradiol product. b(4)

4.1 Sources of Clinical Data

This NDA application consists of 80 volumes. NDA 22-014 is a *paper* submission in the Common Technical Document (CTD) format with the exception of Item 11 (Case Report Tabulations) which is submitted in electronic format (a CD-ROM) was provided in Module 1 of the archival copy). The proposed package insert is formatted according to FDA's January 2006

draft Guidance (Labeling for Human Requirements) and is provided in SPL format on a CD-ROM in Module 1.

4.2 Tables of Clinical Studies

The following reviewer generated table summarizes the pivotal trial (EST-01) and two Phase 1 pharmacokinetic studies (EST-02, EST-06) used to support the indication of relief of vasomotor symptoms.

Table 1: Summary of Clinical Studies

Study ID	No Centers	Study Start/Status Enrollment goal/actual	Design	Study Treatment (Duration)	Study Objective	No. Subjects (entered/completed	Gender Mean age (range)	Diagnosis/Inclusion Criteria	Primary Endpoint (s)
EST-01	43-US	Dec17-2004 Completed March 9/2006	Phase 3, multi-center, randomized,double-blind, placebo-controlled; Six parallel arms (three treatment, three placebo)	Estradiol 3-spray Estradiol 2-spray Estradiol 1-spary Placebo 3-spray Placebo 2-sprays Placebo 1-sprays	Efficacy & Safety	76/69 76/61 77/68 76/57 76/64 77/58	Female 52.0-53.5 (36-76)	Vasomotor Symptoms (8 moderate-to-severe hot flushes a day or a minimum of 56 per week)	Mean change in the number and severity of hot flushes
EST-02	Single center	April 26, 2005 to July 3, 2005	Phase 1 Single center randomized, open labeled, parallel group;	Three treatment arms		72/ 24 per treatment arms 3-spray 24/24 2-spray24/23 1-spray 24/24	Females	Healthy, naturally or surgically postmenopausal women, 40-65 years of age, with no history of clinically significant medical disorders	Steady state pK of estradiol and estrone
EST-06	Single center	September 14, 2005 to November 15, 2005	Phase 1, Single center, open-label	20 female subjects with estradiol spray20 male subjects to test skin-skin transfer	pK parameters; estradiol transfer; effect of sunscreen time; for estradiol spray to dry	40/40	20 postmenopausal females 40-65 years of age, - 20 males 35-65, years of age	20 Healthy, postmenopausal women, with no history of clinically significant medical disorders 20 healthy adult males, for the skin-to-skin transfer segment of the study	

Summary Tables, Module 2 Volume 1&2

4.3 Review Strategy

This review was conducted utilizing the following strategy:

- An overview of the total clinical documents with emphasis on study EST-01; review studies EST-02 and EST-06
- Review electronic format (a CD ROM is provided in Module1 that containing Class Labels and Labeling; Case Report Tabulations are also presented)

4.4 Data Quality and Integrity

There were no Division of Scientific Investigation (DSI) audit processes sought under this NDA. The reason for not seeking a DSI audit is that this product is not an NME, data appeared to be appropriately analyzed; source documents reviewed were found to be consistent with what was presented in the text of the document.

4.5 Compliance with Good Clinical Practices

Two Phase 2 studies (EST-02 and EST-06) and one Phase 3 study (EST-01) were performed according to the versions of the Declarations of Helsinki current at the time of the study. Adequate informed consent was obtained; there were no site-specific issues identified by this reviewer; protocol violations were appropriately identified and this study is acceptable to world-side standards.

4.6 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with clinical investigators as recommended by the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. There were no questions raised about the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The sponsor performed 2 pharmacokinetic studies (Studies EST-02 and EST-06).

Study EST-02 was a single-center, randomized, open label, parallel group study of 72 healthy naturally or surgically menopausal women. Women (aged 40 to 65 years) were randomly assigned to receive one of three dose levels (24 subjects per treatment arm) of estradiol metered-dose spray (MDTS) applied to the inner forearm of the same arm once daily for 14 days. The three treatments A, B and C were one, two and three 90μL sprays, respectively of estradiol 1.7% MDTS. Inclusion criteria are acceptable.

The objective of this study was to determine the steady-state pharmacokinetic parameters of 1.7% MDTS applied to the forearm of healthy postmenopausal women. The following are the mean unadjusted steady state serum pharmacokinetic parameters of estradiol and estrone following daily topical application of estradiol MDTS on day 14:

Estradiol (pg/ml)	C_{max} 1-spray (31.2), 2-sprays (46.1), 3-sprays (48.4)
	C_{min} 1-spray (10.3), 2-sprays (16.4), 3-sprays (18.9)
	C_{aver} 1-spray (17.8), 2-sprays (28.2), 3-sprays (29.5)
Estrone pg/ml)	C_{max} 1-spray (47.1), 2-sprays (58.4), 3-sprays (67.4)
	C_{min} 1-spray (29.0), 2-sprays (39.0), 3-sprays (44.1)
	C_{aver} 1-spray (35.5), 2-sprays (48.7), 3-sprays (54.8)

In this same study the sponsor concluded that dose proportionality for the 1-spray, 2-spray and 3-spray dosages for AUC $_{(0-24)}$ was inconclusive and that the C_{max} was not dose proportional. The clinical pharmacology reviewer concurred with this assessment.

There were 6 reported AEs in 3 subjects. There were no SAEs, discontinuations due to an AE, no interruptions of study medication due to an AE and no deaths in this study.

Study EST-06 was a single center, open-labeled study in 20 subjects who received three-90 µg sprays of estradiol MDTS for18 days. In addition, 20 healthy male subjects participated on Days 1-3 of this study. The objectives of this study were:

1. To study possible transfer of estradiol to persons who may contact (skin-to-skin transfer) the application site off the treated individual.
2. To study the influence of application site washing at 1 hour post application.
3. To study the effect of sunscreen use at the application site at 1 hour prior to and 1 hour after application.
4. To study the time required for estradiol MTDS spray to dry by visual inspection.

Results are as follows:

1. For skin to skin transfer the amount of estradiol transferred was minimal (<4%).
2. Washing increased the AUC and C_{max} of estradiol. Approximately 5% of estradiol was detected in washed material.
3. Sunscreen applied 1 hour prior to or 1 hour after Evamist™ application did not significantly affect the pharmacokinetics of estradiol; there was an 11% reduction in exposure when sunscreen was applied 1 hour post dose.
4. The average drying time for 1 spray of Evamist™ was 90 seconds (median time 67 seconds).

There were 4 reported AEs in 4 subjects. Body ache was experienced by 3 subjects and one subject experienced lower back pain. There were no SAEs, dose interruptions, discontinuation due to an AE and no deaths in this study.

5.2 Pharmacodynamics

No pharmacodynamic studies were performed with Evamist™.

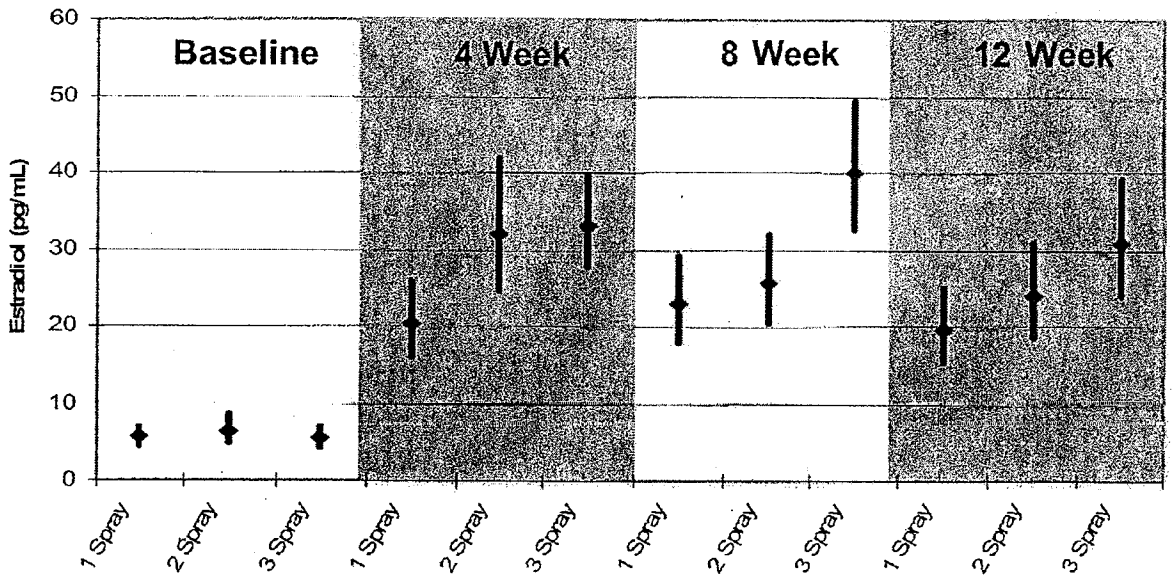
5.3 Exposure-Response Relationships

Serum estradiol and estrone levels were determined at baseline and at weeks 4, 8 and 12 following initiation of treatment. Samples were obtained well before the peak levels (18-22 hours after dosing) and provide a reasonable estimate of the average concentration (C_{aver}) of each analyte during the 24-hour dosing cycle.

Estradiol levels were increased in all 3 treatment groups. In the 3-spray group the mean post-treatment (95% CI) serum estradiol levels ranged from *30.7* (24.1, 39.1) pg/mL to *40.1* (32.6-49.4) pg/mL. In the 2-spray group, mean (95%) CI) serum estradiol levels ranged from *24* (18.6-31.0) pg/mL to *32.1* (24.7-41.8) pg/mL. In the 1-spray group mean 95%) CI) estradiol levels ranged from *19.5* (15.3-25) pg/mL to *22.9* (17.9-29.3) pg/mL. Serum estradiol levels appear to increase with dose although no dose proportionality analysis was conducted in this trial. Serum levels reached steady state by week 4 and levels remained relatively constant for the duration of the study.

The following figure shows the geometric mean of unadjusted estradiol levels at weeks 4, 8 and 12. Mean (95%) CI) baseline estradiol levels were uniform across the treatment groups:

Figure 1: Mean (95%)* Unadjusted Serum E2 Levels with Estradiol Transdermal Spray

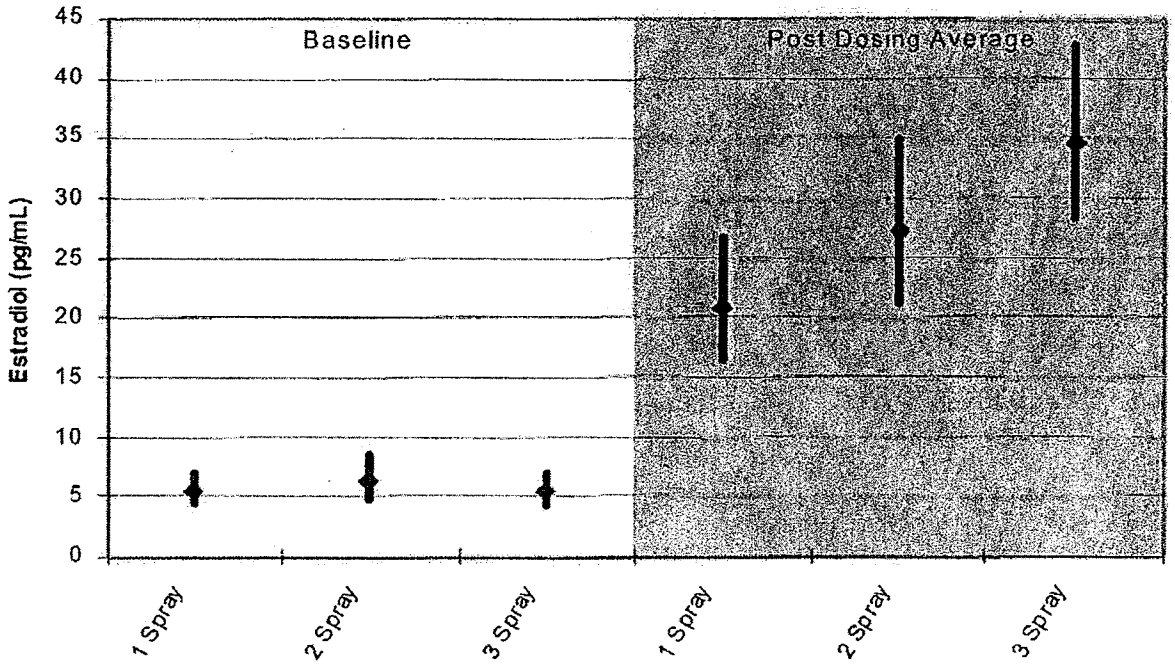


* Geometric mean; 95% CI = 95% Confidence Interval

Note the wide confidence intervals for each dosage. Also note fairly uniform estradiol level for the one spray dose; note greater variability in the 2-spray and 3-spray dosages at weeks 4, 8 and 12.

The following figure shows a *post-hoc analysis*, post-dosing average serum estradiol results for weeks 4, 8 and 12 that are combined to provide an overall estimate of steady state serum levels

Figure 2: Mean (95%CI)* Post Dosing Serum E2 Levels with Estradiol Transdermal Spray



* Geometric mean; 95% CI = 95% Confidence Interval. Post-dosing averages represent averages of the means for the week 4, 8 and 12 time periods.

For the 1 spray dose the average estradiol serum level is 20.9(16.4-26.8) pg/mL, for the 2-spray dose the average estradiol serum level is 27.2(21.2-35.0) pg/mL and for the 3-spray group the average estradiol level is 34.6(28.2-42.7) pg/mL. Note the wider CI with the 3-spray and 2-spray dosages.

Estrone levels were elevated in the estradiol treatment groups and *were less variable than the estradiol levels*; estrone levels were also higher in higher dose groups. Mean (CI) baseline estrone levels [18.6 (16.0-21.50pg/mL to 20.2 (17.6-23.2) pg/mL] increased to steady state levels of 49.4 (44.5, 54.9) pg/mL to 55.5 (49.3, 62.7) pg/mL following treatment with 3 sprays/day; 2-sprays/day levels were 41.7 (35.9, 48.5) pg/mL to 46.3 (39.9, 53.9) pg/mL ; one spray/day levels increased from 33.3 (29.3, 37.8) to 38.2 (34.1, 42.9) pg/mL.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Evamist™ is indicated for the treatment of moderate to severe vasomotor symptoms in postmenopausal women.

6.1.1 Method

The general method used to review hormones in the treatment of moderate to severe vasomotor symptoms has been to review clinical trial data accrued during 12 weeks of treatment. Usually there is a 2-4 week run-in period that establishes a baseline number of vasomotor symptoms. The subject should have at least 50-60 moderate-to-severe hot flushes per week or a minimum of 7-8 moderate-to-severe hot flushes per day during the baseline period for entrance into the treatment period. Mild symptoms have not been included in the primary efficacy analysis.

6.1.2 General Discussion of Endpoints

In January 2003 the Draft HT Guidance was published. In the Draft Guidance the following four co-primary efficacy variables were recommended to establish efficacy:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

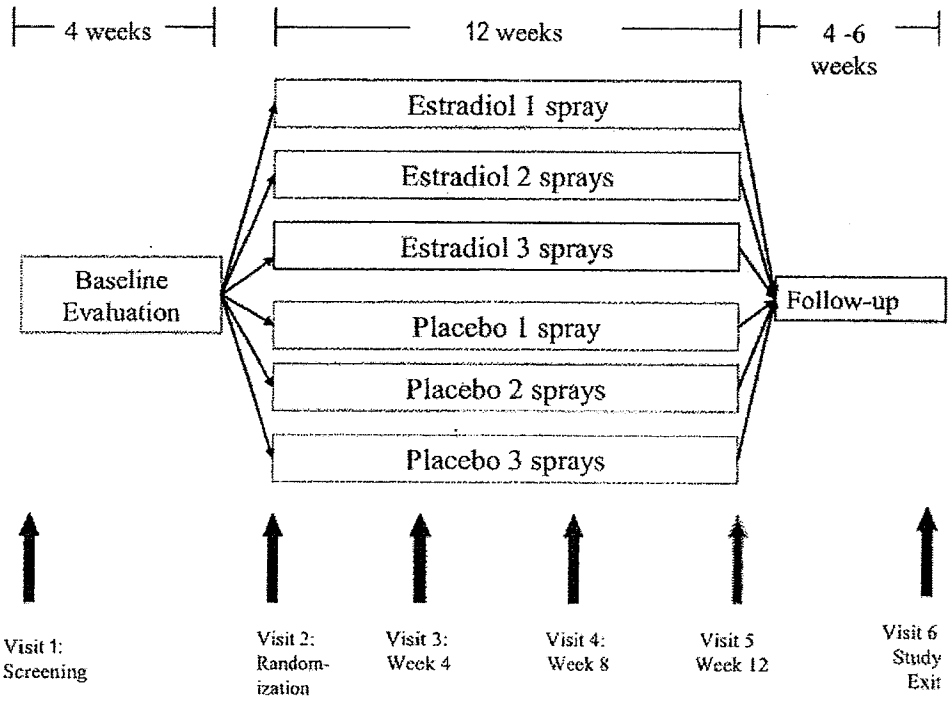
6.1.3 Study Design

Study EST-01 was a 12-week randomized, double-blind, multi-center, placebo controlled trial to evaluate the safety and efficacy of estradiol transdermal spray (1, 2 or 3 sprays daily) for treatment of vasomotor symptoms in symptomatic postmenopausal women. For approval in the US a 3-month safety and efficacy trial is sufficient.

6.1.4 Efficacy Findings

The primary objective of study EST-01 was to evaluate the safety and efficacy of 1, 2 or 3 sprays of estradiol transdermal sprays in the relief of moderate to severe vasomotor symptoms associated with the menopause. Secondary objectives were the reduction in mild, moderate and severe hot flushes at weeks 4, 8 and 12 and the frequency and severity of moderate and severe hot flushes at week 8.

Figure 3: Trial Design of Study EST-01



The design of study EST-01 and the efficacy and safety endpoints employed were to conform to the 2003 Draft HT Guidance.

The estradiol doses (1, 2 and 3 sprays) were chosen to provide a range of exposures to allow assessment of safety and efficacy. Dose selection was based on the results of previous studies with estradiol transdermal spray that showed increases on average serum estradiol concentrations of 30-35 pg/mL after multiple doses of two 90 µL sprays per day. Based on the expected exposure of the 1 spray dose and the published literature data for currently marketed transdermal estrogen products, *the one spray dose was not expected to be a fully effective dose.*

Throughout treatment both the study site and the subject were blinded as to treatment group randomization (active or placebo); both site personnel and the subject were aware of the number of sprays applied each day.

The following table shows the Trial Flow Chart

Table 2: Trial Flow Chart

	Pre-treatment	Treatment Period				Post-treatment
Visit	**1**	**2**	**3**	**4**	**5[g]**	**6**
Study Week (from randomization)	**−4**	**0**	**4 ± 1 week**	**8 ± 1 week**	**12± 1 week**	**16-18 ± 1 week**
Informed Consent/Authorization	x					
Inclusion/Exclusion Criteria	x	x				
Demographic Data	x					
Medical History	x					
Vital Signs	x	x	x	x	x	x
Complete Physical Examination	x				x	
Bimanual Pelvic Examination	x				x	
Breast Examination	x				x	
Concomitant Medication(s)	x	x	x	x	x	x
Cervical Smear (PAP)[c]	x[j]				x	
Mammogram[d]	x[j]					
Endometrial Biopsy[e]	x[j]				x	
Hematology	x[j]				x	x
Biochemistry	x[j]				x	x
Coagulation Parameters[a]	x[j]				x	
Lipid Profile[b]	x[j]				x	
Estradiol & FSH Screen	x[j]					
Urinalysis	x[j]				x	x
Urine Pregnancy Test	x[j]					
Distribution of Diary Cards	x	x	x	x		
Estradiol, Estrone & Estrone Sulfate Serum Levels[i, k]		x	x	x	x	
Collection of Diary Cards		x	x	x	x	
Distribution of Test Medication		x	x	x		
Local Tolerability (Draize)		x	x	x	x	
Greene Climacteric Scale		x			x	
Distribution of MPA 5 or 10 mg[f]					x	
Adverse Events		x	x	x	x	x[h]

a: Coagulation parameters included Factor V Leiden, antithrombin III, fibrinogen, prothrombin time, protein C and protein S.
b: Lipid profile included total cholesterol, LDL, HDL, triglycerides and lipoprotein (a).
c: A baseline cervical smear was not required if previous acceptable results were available from a smear taken during the last 6 months.
d: Screening mammograms were not repeated for women who had documentation of an acceptable mammogram within 9 months of screening.
e: Endometrial biopsy was performed for women with an intact uterus.
f: MPA was dispensed only for women with an intact uterus.
g: Visit 5 evaluations were to be carried out for subjects who withdrew from the study prior to completing the treatment course.
h: To be followed until resolved or at least stabilized.
i: Estradiol, estrone and estrone sulfate tests (at visits 2, 3, 4, and 5) were performed at a specialty laboratory and were not to be sent to the central laboratory used for screening and end-of-study laboratory tests.
j. Bolded screening tests and procedures represent those that were performed after the prospective subject had successfully completed screening for medical history and the basic physical examination, including pelvic and breast examinations.
k. All available paired samples (visits 2 and 5) with adequate volume in the 3-spray groups from eligible sites were tested for SHBG levels.

The trial comprised a total of 6 visits. See Table 2: Trial Flow Chart above

Screening (Visit 1)

At screening prospective subjects provided written informed consent. The subject's medical history (including demographic data and concomitant medications) was obtained, and a complete physical examination (including pelvic and breast examinations) was performed. Blood and urine samples were obtained and vital signs were monitored. A Pap smear was performed if previously acceptable results were not available from the smear obtained within the previous 6 months. A mammogram was performed (if non-documentation was available of acceptable results from a previous mammogram within 9 months) and the subject underwent an endometrial biopsy during or following the screening visit. Subjects were given a study diary and instructed to record all hot flushes on a daily basis during a 4-week (± 1week) baseline period.

Visit 2 (End of baseline Run-In Period)

Study diaries were reviewed and the number of moderate and severe hot flushes determined. Subjects with an average of ≥ 8 moderate or severe hot flushes per day (≥ 56 per week) were eligible for randomization into the treatment portion of the study. A blood sample was obtained for hormone evaluations. Vital signs were checked, concomitant medications monitored, and a local skin tolerability assessment obtained. Subjects completed the Greene climacteric scale form and were given the assigned applicator(s) and instructed in the use of the applicator. The first dose of test material was applied at the clinic. Instructions for completing the diary were reviewed and a new diary was dispensed.

Visits 3 and 4 (Week 4 and 8)

At the end of 4 weeks (± 1 week) subjects returned to the site for visit 3. Applicators used during the first treatment period were returned to the site; diary entries were reviewed and summarized by site personnel. Adverse events were evaluated, local tolerability assessed, vital signs obtained and concomitant medications monitored. A blood sample for hormone evaluation was obtained. Instructions for the administration of test material and for diary completion were reviewed, and a new diary was dispensed to the subject. Additional applicator(s) were dispensed as required. These procedures were repeated at visit 4 at the end of 8 weeks of treatment (± 1 week).

Visit 5 (Week 12)
Visit 5 was the end-of-treatment visit (occurred at week 12 [± 1 week]). Site personnel collected diaries, summarized diary entries and collected used applicators. Adverse events were evaluated and administration site tolerability was assessed. Subjects completed the Greene climacteric scale questionnaire and provided an overall evaluation of the effect of treatment. Blood (including hormone studies) and urine test were repeated, a completed physical examination (including pelvic and breast examinations) were performed, and a Pap smear was obtained. An endometrial biopsy was obtained (during or following visit 5). Subjects with an intact uterus were prescribed a daily dose of medroxyprogesterone acetate (MPA) 5 or 10 mg for the first 2 weeks after treatment of unopposed estrogen to counterbalance the effect of estrogen-induced endometrial proliferation.

Visit 6 (Follow-up)
The follow-up visit occurred 4 weeks (± 1 week) after completion of treatment or 4 weeks (± 1 week) after MPA administration was completed for subjects with an intact uterus. Following scheduled testing and adverse event monitoring, the subjects were discontinued from the study.

Reviewer's Comment
Recorded visits are consistent with recommendations in FDA's Draft HT Guidance. Of interest is the sponsor's management of subjects with an intact uterus. Estradiol was given in an unopposed manner; therefore, all subjects received MPA at the end of study to counterbalance the effect of unopposed estrogen on the endometrium.

Trial Population
Approximately 444 subjects (74 per group) were intended for randomization. A total of 458 subjects were randomized; 454 subjects received at least 1 dose of test material and were included in the intent-to- treat (ITT)/ safety analysis; 437 were included in the modified ITT analysis, and 428 were included in the efficacy evaluable (EE) analysis.

Study Population

Inclusion Criteria

- An approved informed consent form was signed.
- Subject should be postmenopausal. Postmenopausal was defined as having 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels > 40IU/L or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy as documented by surgical records and/or pathology report.
- A history of frequent moderate to severe hot flushes (estimated average minimum of 8 moderate to severe hot flushes per day),
- Age 35 years or older,
- An adequate washout period from estrogen-containing products prior to obtaining any baseline assessments in prospective subjects who have been previously treated for

postmenopausal symptoms. The minimum washout period was 1 week for prior use of vaginal hormonal products (Estring®, creams, gels) 4 weeks for prior transdermal estrogen alone or estrogen/progestin products and FemRing®, and 8 weeks for oral estrogen and/or progestin therapy or prior intrauterine progestin therapy.

- Acceptable cervical smear (Pap smear). An acceptable cervical smear was defined as a smear in which no dysplastic or malignant cells were identified. A cervical smear need not have been repeated for subjects who documentation of a previous acceptable Pap smear had taken during the 6 months prior to study screening.
- Acceptable mammogram and clinical breast examination at screening. An acceptable mammogram was defined as a mammogram in which no masses or other findings were identified that was suspicious of malignancy. A screening mammogram was not required for women who had documentation of an acceptable mammogram within 9 months of study screening. An acceptable breast examination was defined as no masses or other findings that were suspicious of malignancy.
- The ability and willingness to complete daily menopausal symptom diary records and to return to the study center for the scheduled follow-up visits for the duration of the study, and
- In a women with a uterus, acceptable results from a screening endometrial biopsy. (Acceptable results on endometrial biopsy were defined as a lack of hyperplasia or cancer).

Exclusion Criteria

- Known hypersensitivity to estrogens or progestins or any history of abnormal drug reaction to estrogens or progestins,
- Clinically relevant cardiovascular, respiratory, hepatic, neurological, endocrine, hematologic or other major systemic diseases as revealed by medical history, physical examination and/or laboratory assessments, which in the opinion of the investigator precluded the safe participation in the protocol. Prospective subjects with a history of insulin-dependent diabetes or uncontrolled epilepsy were excluded,
- Use of progestin implants, estrogen alone injectable estrogen pellet therapy or progestin injectable drug therapy within year prior to screening,
- Body mass index (BMI) > 35kg/m^2,
- Current or past history of clinically significant psychiatric disease or severe depression,
- Current history of gallbladder disease (e.g. cholestasis),
- Triglyceride values of ≥ 3.4 mmol/L (≥ 300mg/dL) where it was considered clinically relevant because there was a family history of hypertriglyceridemia,
- Uncontrolled hypertension (diastolic blood pressure ≥ 95mmHg and/or systolic blood pressure ≥ 180mm Hg). Hypertensive patients normalized under stable medications were suitable for inclusion.
- Current or previous documented history of coagulopathy, thrombophlebitis, thrombosis or thromboembolic disorders,
- Previously documented liver dysfunction in which parameters of liver function failed to return to normal or impaired liver function, as shown by but not limited to serum

bilibrubin, aspirate transaminase (AST) or alanine transaminase (AST) exceeding 2-fold upper limit of normal at the screening visit,

- History of porphyria,
- Current or past history of cutaneous contact allergy to adhesives, cosmetics or topical medications including sunscreens,
- Current history of any active dermatological disease that might interfere with or could modify skin absorption and/or skin tolerance,
- In prospective subjects with an intact uterus, evidence of clinically significant gynecological disorders including endometrial polyp, endometrial hyperplasia, uterine fibroid, malignancy or infection revealed by pelvic examination, and endometrial biopsy. Subjects with small fibroids, which were asymptomatic and deemed by the investigator not to require surgical treatment, were not excluded,
- In prospective subjects with an intact uterus, failure to obtain an adequate endometrial sample at screening biopsy because of technical or administrative reasons and/or any contraindication to planned assessments, e.g. biopsy,
- Abnormal genital bleeding of unknown etiology in the last 6 months,
- Pregnancy, (If the prospective subject had undergone a hysterectomy or bilateral tubal ligation or was 55 years of age or greater and had experienced cessation of menses for at least 1 year, a pregnancy test was not required.)
- Evidence of clinically significant breast disease revealed by breast examination (palpation) or detected by mammogram,
- Current or previously documented history of malignancy (except completely resected cutaneous basal and squamous cell carcinoma) or estrogen dependent neoplasia,
- Treatment with any investigational or experimental drug within 4 weeks prior to screening,
- Current history of drug or alcohol abuse,
- Any condition that, in the investigator's opinion, would have caused this study to be detrimental to the subject or that made the subject unsuitable to participate in or to complete the study, and
- Dubin-Johnson or Rotor Syndrome.

Reviewer's Comment
Inclusion and exclusion criteria are consistent with previous studies that assess treatment of vasomotor symptoms.

Randomization Requirements
Following the baseline run-in period, subjects were eligible for randomization to treatment if they met the following criteria:

- Demonstrated compliance with protocol requirements as evidenced by completion of at least 14 days information in the subject diary,
- A mean total frequency of $\geq$ 56 moderate to severe hot flushes per week during the baseline evaluation period. (A moderate hot flush was defined as a sensation of heat with sweating but ability to continue activity. A severe hot flush was defined as a

sensation of heat with sweating, causing discontinuation of activity. A mild flush was defined as a sensation of heat without sweating),

- Continued to fulfill all of the inclusion/exclusion criteria, including those requiring laboratory testing or physical examination.

Removal of Subjects from Therapy or Assessment

The predetermined reasons for removing subjects from therapy were:

- request by the subject to withdraw from therapy (withdrawn consent),
- Intercurrent illness that required discontinuation of treatment per protocol,
- A severe or serious adverse event, that in the opinion of the investigator, precluded completion of study participation,
- Investigator's judgment to protect the subject's best interest,
- Pregnancy,
- Poor compliance, that in the opinion of the investigator, could have rendered the subject's results non-evaluable, and
- Termination of the trial.

Reviewer's Comment

Randomization requirements and predetermined reasons for removal of subjects from the trial are consistent with trials evaluating treatment of vasomotor symptoms.

Identity of Investigational Product

Estradiol transdermal spray and placebo solutions were manufactured by ——— and were packaged and distributed to clinical sites by ——— ——— Each applicator of estradiol transdermal spray or placebo solution had a unique number that allowed the tracking of the individual applicator during the conduct of the trial. b(4)

Estradiol transdermal spray is a single-phase solution containing estradiol USP (17-β-estradiol), octisalate and alcohol ——— Octisalate is a penetration enhancer and is a common component of sunscreens. b(4)

All study site personnel and subjects were blinded as to the subject's treatment group randomization (active or placebo). The labeling did not identify the study drug. Test material identity was printed under the occluded portion of the label that was removed from the applicator box and retained at the site. Blinding could be broken only if considered necessary by the investigator to treat the subject for an adverse event or other medical emergency. In such instances, site personnel could obtain the identity of the study treatment by scratching the occluded label. If unblinding occurred, the site was required to notify the sponsor by telephone within one working day following the breaking of the blind.

The occluded labels were verified by study monitors and retrieved by the sponsor at the completion of treatment.

Concomitant Therapy
The use of medications with known or suspected influence on the relief of symptoms related to estrogen deficiency such as other estrogen and/or progestin preparations, including complementary therapies such as phytoestrogens, soy supplements, ginkgo and ginseng was prohibited. Subjects taking such medications were required to complete an 8-week washout period to enrollment.

The use of drugs that interact with estrogens such as barbiturates, benzodiazepines, rifampicin, phenylbutazone compounds, griseofulvin and metoprolol was prohibited. In addition, use of dopaminergic or antidopaminergic drugs, digitalis preparations, psychotropic medications [including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRI), narcotic analgesic and certain antihistamines, including diphenhydramine, was prohibited throughout the course of the study.

Subjects were to report all concomitant medications, including over-the-counter products, herbal medications and nutritional supplements. Subjects were instructed to record any changes in concomitant medications during treatment in their diary cards and were questioned regarding concomitant medications at each site visit.

Treatment Compliance
With the exception of the initial dose of study medication, all treatments were administered by the subject at home without site supervision. Site personnel assessed treatment by reviewing subject diary record and by querying the subject regarding possible missed doses at each site visit during treatment.

In addition to the compliance checks by site personnel, an audit of returned clinical supplies was conducted at the packaging facility [redacted] by Vivus personnel upon completion of the study. During the audit, all drug applicators from a random sample of 23 subjects, representing 5% of the overall drug supply, were disassembled. Residual volume was measured in these applicators and compared to the expected residual volume that would be predicted from each subject's diary. b(4)

Changes in the Conduct of the Study or Planned Analyses
Protocol Amendments
The initial study protocol was amended 5 times. The following paragraphs document changes to the initial protocol.

The first amendment (November 22, 2004) changed the number of treatment groups from 4 to 6 to allow for the inclusion of a higher treatment dose (3 sprays). The sample size was increased from 296 to 444 randomized subjects and the possible number of site increased from 25-35 to 35-50 to accommodate this change. The protocol had been reviewed by the Agency but had not been initiated when this amendment was made.

The second amendment (February 11, 2004) added an age range criterion to the entrance criteria; protein C was added to the laboratory testing and concomitant medication requirements were clarified; a Global Assessment question to evaluate treatment effect was added. The statistical section was modified to permit pooling of placebo groups if baseline characteristics were found to be similar. The definition of a severe hot flush was modified from "...sensation of heat with sweating causing cessation of activity" *to* "a sensation of heat and sweating, causing you to discontinue activity."

The third amendment (May 6, 2004) modified the dosage and administration of test material to allow sites to distribute applicators as needed for adequate dosing, with the number of applicators dispensed being group and visit dependent.

The fourth amendment (November 7, 2004) was implemented on January 12, 2006. This amendment modified the statistical section to clarify the use of the Hochberg step down procedure in the primary analysis, described how missing values would be imputed for efficacy analyses, added race as a subgroup for analysis and allowed for the evaluation of additional subgroups. It also provided for the evaluation of SHBG levels at baseline and the end of treatment for subjects in the 3-spray groups.

The fifth amendment (April 26, 2006) was an administrative amendment, implemented after subject treatment under the protocol had ended but prior to database lock and unblinding. In this amendment, the statistical section was modified to provide detail on the pairwise comparisons in the primary efficacy evaluation as requested by the Agency. In addition, the volume of a spray dose was changed from 91μL to 90μL to correct an error in the initial protocol.

Planned Analyses
Following conversations with the Agency, the initial SAP was modified on April 26, 2006 to include *additional supplemental endpoints* relating to the frequency and severity of vasomotor symptoms that would serve to clarify the relationship of treatment to effect. These were:

- The mean change in frequency and severity of moderate to severe vasomotor symptoms from run-in period to each week up to week 12;
- The mean change in frequency and severity of mild, moderate and severe vasomotor symptoms from run-in period to each week up to week 12;
- The mean change in the severity index of moderate and severe vasomotor symptoms from run-in period to each week up to week 12;
- The mean change in severity index of mild, moderate and severe vasomotor symptoms from run-in period to each week up to week 12; and
- The percent reduction of frequency and severity for each subject from run-in period to each week up to week 12.

Reviewer's Comment
Protocol amendments 1-3 were discussed with the sponsor prior to actual submission of the amendments. Protocol amendments 4 and 5 were discussed with the clinical team and the statistical team; amendment modifications are acceptable.

Efficacy

All primary and secondary efficacy results were based on the subject's reports in the daily diary of the number and severity of hot flushes during the baseline and treatment periods. The primary efficacy analyses calculated the severity score of moderate to severe hot flushes. The severity score for moderate to severe hot flushes is defined as:

(2 x number moderate hot flushes + 3 x number of severe hot flushes)/
(number of moderate + number of severe hot flushes).

Additionally, as per the Agency's request, the weekly severity score for mild, moderate and severe hot flushes is also presented as a *secondary endpoint* and is defined as:

(1 x number of mild + 2x number of moderate + 3x number of severe hot flushes)/
(number of mild + moderate + number of severe hot flushes).

For all severity score calculations, on days when no moderate or severe hot flushes for estimate of moderate/severe hot flushes and there were no mild, moderate or severe hot flushes for estimation, a severity score of 0 was assigned.

For the purposes of efficacy analyses involving diary data, day 0 was defined as the day the first dose of study drug was administered. Day 1 is defined as the day after the first dose of study drug administration. Week 4, weeks 8 and 12 were defined as days 22-28, 50-56 and 78-84 days, respectively. Run-in (or baseline) calculations were determined by considering the 14 days prior to first drug administration in which the diary was completed.

Prior to initiating therapy and the end of treatment, subjects completed an evaluation to assess the effect of treatment on climacteric symptoms using the Greene Climacteric Scale.

At the end of treatment visit, subjects also responded to a Global Assessment question of the overall effect of treatment as follows:

How would you describe the effect of study treatment on your menopausal symptoms (hot flashes and sweating)? (Markedly improved, improved, no change, worse, markedly worse).

Safety

All subjects in the ITT population were included in the safety analysis. The investigator adverse event terms were mapped to preferred terms and system organ classed using the MedDRA dictionary, Version 7.1. The total number of subjects reporting treatment-emergent events was summarized for each treatment (within each group) by system organ class and by preferred term. In addition each adverse event was summarized by severity and relationship to study drug. If more than one adverse event was mapped to the same preferred term, it was counted once per subject using the event with the highest severity and closest relationship to study drug.

Descriptive statistics of clinical laboratory assessment changes were presented for screening and completion of each treatment period. In addition, shift tables were presented to assess abnormal

laboratory values over time. Laboratory parameters were classified as low, normal or high; subject counts of shifts tables from baseline values were also presented.

Vital signs were collected at each visit. A physical examination was performed and an endometrial biopsy and cervical smear specimens were collected at screening and at end of study. Findings were classified as either normal or abnormal and results presented in shift tables and listing.

Application site tolerability was determined using the Draize scale score.

Concomitant medications were linked to generic terms and Anatomical Therapeutic Chemical (ATC) classes using the WHO dictionary, Version 4.3. The total number of subjects reporting concomitant medications was summarized for each treatment group by ATC class and generic term. If more than 1 concomitant medication was mapped to the same generic term, it was counted once per subject.

Statistical Considerations
All analyses were performed using SAS® version 8.2 on a PC platform. Statistical test to evaluate treatment differences were 2-sided with a significance level of 5% ($\alpha = 0.05$) and were declared statistically significant if the calculated p-value was ≤ 0.05. Treatment by region interaction was performed at the 0.10 level.

Statistical methods are described in the protocol (Appendix 16.6.6) and describe in detail the statistical analysis plan (SAP) (Appendix 16.1.9) that was finalized before the database was locked and study drug were unblinded.

Three analysis populations were employed:

- Intent-to-treat (ITT)/safety population (including all subjects who were randomized and received at least one dose of study medication).
- Modified ITT population (including subjects who received at least 1 dose of study medication and had a minimum of at least 1 post dose diary data)
- Efficacy evaluable (EE) population [subjects from the ITT/safety population who did not have any major protocol violations that could affect treatment outcomes or treatment evaluations. This included: < 70% compliance for dosing (as evaluated by reported missed doses) in months 1 (weeks 1-4) and 3 (weeks 9-12); < 50% compliance for diary data from randomization to week 4 or randomization to week 8 or randomization to week 12; initiation of treatment during the study with a medication that might confound assessment of 1 or more primary endpoints, and use of incorrect dose throughout treatment.]

Analyses for the primary, secondary and supplemental efficacy endpoints, including climacteric variables and overall assessment, were conducted in all 3 populations. Safety analyses were performed using the ITT/safety population.

Primary Efficacy Analyses
The mean change in frequency and severity of moderate to severe vasomotor symptoms from baseline to weeks 4 and 12 were compared between treatment groups using the analysis of covariance model (ANCOVA) where change from run-in period was the dependent variable, treatment region, and treatment by region interaction were the independent variables and baseline score the covariate.

Three pairwise comparisons were of primary interest:

1 Spray	Estradiol 1.7% transdermal spray dose, one 90µL spray versus placebo dose, one 90µL spray
2 Sprays	Estradiol 1.7% transdermal spray dose, two 90µL sprays versus placebo dose, two 90µL sprays
3 Sprays	Estradiol 1.7% transdermal spray dose, three 90µL sprays versus placebo dose three 90µL sprays

Three separate ANCOVA models were run on the above pairwise comparisons of interest following the *a priori* sequence of 3 sprays, 2 sprays and 1 spray.

The 3-spray (estradiol/placebo) arms were compared first; then the 2-spray arms, followed by the 1-spray. The type 1 error rate was set at the 0.05 level at each dose comparison, and once a statistical test failed to reject the null hypothesis for any of the 4 endpoints, testing was curtailed at that point from a confirmatory/regulatory perspective.

Secondary efficacy analyses
The mean change in frequency and severity of moderate to severe vasomotor symptoms from run-in to week 8 was analyzed through week 12 was evaluated as was the mean change in frequency and severity of mild, moderate and severe vasomotor symptoms from run-in to each week up through week 12. These analyses of changes in frequency and severity of vasomotor symptoms from run-in period to various time points were carried out in the same manner as the co-primary endpoints.

Sample Size Calculations
An estimated sample size of approximately 444 subject's randomized (74 subjects per treatment group) was employed.

The sample size determination was based on the estimated change in the mean daily frequency of moderate to severe vasomotor symptoms from baseline to week 4 and week 12. It was assumed that subjects would have an average of 11 moderate to severe hot flushes per day at baseline and that with treatment there would be a mean change from baseline of 5 moderate to severe hot flushes in the placebo group and 9 moderate to severe hot flushes in the active groups, results in a mean treatment difference of about 4 moderate to severe hot flushes per day. A sample size of 48 subjects in each 4 treatment groups was found to give a 90% power to detect a contrast of 4 with a scale of 1.41 when the common standard deviation was 6 when comparing the placebo group(s) to the active group(s) using a 0.05 level 2-sided test in a one-way analysis of variance.

The severity of hot flushes was assumed to have a similar or lower effect size as the number of hot flushes (delta = 1.55, SD =2.3) and hence the sample size estimate for the frequency of hot flushes was considered sufficient to cover the severity of hot flushes endpoint.

It was estimated that approximately 35% of subjects would have some degree of incomplete data. Thus, the total sample size was calculated to be approximately 444 subjects randomized (74 per group).

Disposition of Subjects
A summary of subject disposition is provided in the following Table 3: Subject Disposition and Figure 4: Subject disposition by Treatment Group

Table 3: Subject Disposition

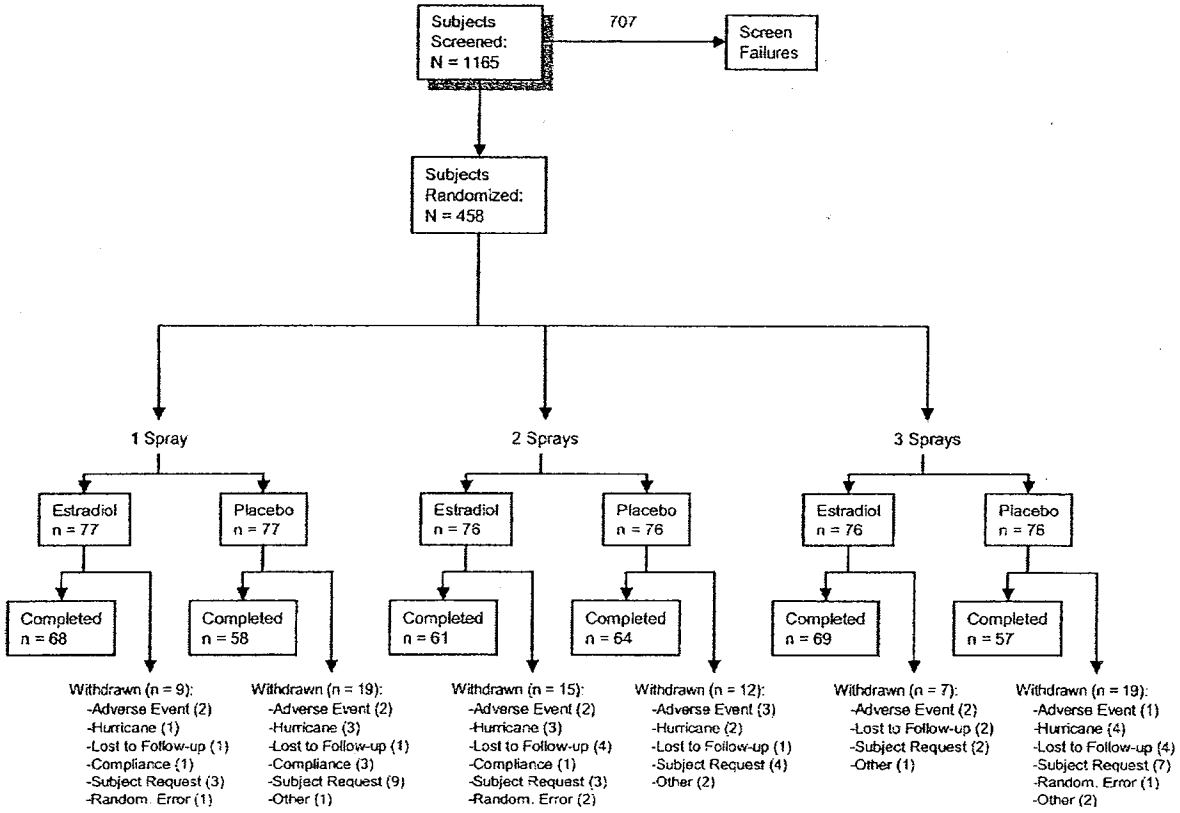
Category	Number of Subjects	Percent (%)*
Enrolled	1165	NA
Screen Failures	707	NA
Randomized	458	100.0
Received at Least One Dose	454	99.1
Withdrawn from Treatment	81	17.7
Completed Study	377	82.3
Reason for Early Termination		
Request by Subject to Withdraw	28	6.1
Lost to Follow-up	13	2.8
Hurricane**	13	2.8
Adverse Event	12	2.6
Poor Compliance	5	1.1
Randomized in Error	4	0.9
Other	6	1.3

* % of subjects randomized
** Hurricane Katrina occurred while this study was in progress and two study sites were directly impacted by the storm.

Seven hundred-seven (707) subjects were screen failures and 458 were randomized into the treatment phase of the study. A total of 454 subjects began treatment in the study (76, 3-spray estradiol; 74, 2-spray estradiol; 76, 1-spray estradiol; 75, 3-spray placebo; 76, 2-spray placebo; 77, 1-spray placebo). Overall, completion rates among subjects receiving estradiol and placebo were 87.6% and 78.5%, respectively.

The following figure 4 shows the disposition by treatment group:

Figure 4: Subject disposition by Treatment Group



Note 81 (17.7%) of subjects were withdrawn from treatment. In the estradiol treatment group 31 subjects (13.7%) were withdrawn with 7, 15, and 9 subjects being from the 3-, 2- and 1-spray groups, respectively. A total of 50 placebo subjects (21.9%; 19, 3-spray; 12, 2-spray; 19, 1-spray) were withdrawn. The most frequent reason for withdrawal was subject request (8, estradiol; 20 placebo); in the estradiol treatment group, 2 subjects in the 3-spray group, 3 subjects in the 2-spray and 3 subjects in the 1-spray group requested to be withdrawn from treatment. In the placebo group 7, 4, and 9 subjects in the 3-, 2- and 1-spray groups, respectively, requested withdrawal from the study during the treatment. Overall, 13 subjects (7, estradiol; 6, placebo) were lost to follow-up and 12 subjects (6 estradiol; 6, placebo) were withdrawn due to adverse events. The study was ongoing during hurricane Katrina and 13 subjects (4 estradiol; 9, placebo) withdrew or were withdrawn from the trial as a direct result of the displacement caused by the storm. Four subjects (3, estradiol; 1, placebo) were withdrawn due to a randomization error, 3 prior to treatment and 1 following 20 days of treatment.

Four randomized subjects were not treated under the protocol. Three subjects (6020126, 6370133, and 6420127) were randomized in error (1-spray, 3-spray placebo, 2-spray estradiol,

respectively) and were withdrawn prior to receiving any treatment. One additional subject (6360124) 2-spray group) requested to be withdrawn prior to treatment.

The sponsor summarized protocol deviations and violations in table 5. This table will be now summarized. There were a total of 248 protocol deviations and violations. Of this total 149 (60.0%) were Out-of-Window study visits; 39 (15.7%) used a prohibited medication(s) during treatment or had an incorrect washout of prohibited medication; 11 (4.4%) use of medroxyprogesterone acetate (MPA) did not conform to protocol requirements; 10 (4.0%) used a prohibited herbal/natural product(s) during treatment or an incorrect washout period; 7 (2.8%) had fewer than 8 hot flushes/ day at randomization; 5 (2.0%) had a BMI greater than 35 kg/m^2; 4 (1.6%) were randomized in error and were withdrawn from the study; 4 (1.6%) began HRT during the follow-up period; 4 (1.6%) had an out of range FSH at randomization; 3 (1.2%) had unintentional unblinding of site personnel or monitor; 2 subjects (0.80%) each had either a mammogram study out of the 9-month window, were randomized with active eczema, had elevated blood pressure at screening or took HRT at screening (or an incomplete washout period). One subject (0.40%) each either took the incorrect dose throughout treatment, were randomized with allergy to a ——), a urinalysis was not obtained at screening or a baseline hormone laboratory test(s) was not obtained. b(4)

In addition, a total of 75 subjects reported missing 1 or more doses of medication during treatment, with the number of missed doses ranging from 1 (32 subjects) to 19 (1 subject).

Throughout the study, waivers were filed to document a question from a site even through no protocol violation or violation was involved, and many of the waivers represent only a discussion with a site regarding a subject. A total of 23 randomization waivers were granted (11, estradiol; 12, placebo).

None of the protocol deviations identified appear to have affected the results of this study, and no data collected from subjects with protocol deviations were excluded from study analyses. None of the waivers granted had any substantial clinical impact on the subjects enrolled into the study.

Reviewer's Comment
A total of 248 subjects with protocol deviations or violations appear to be a high number when taking in the context of 458 subjects who were randomized. However, of these 248 violations/deviations, 149 subjects were Out-of-Window study visits with the remaining 99 subjects comprising more standardized protocol deviations/violations. Furthermore, another 39 subjects used prohibited medications or had an incorrect washout of prohibited medications, and another 11 did not conform to protocol requirements for MPA use.

The following table 4 shows the demographic of subjects in the ITT/safety population

Table 4: Demographics of Subjects in the ITT/Safety Population

Demographic	3 Sprays		2 Sprays		1 Spray	
	Estradiol (N = 76)	Placebo (N = 75)	Estradiol (N = 74)	Placebo (N = 76)	Estradiol (N = 76)	Placebo (N = 77)
Age (yr)						
Mean (SD)	52.3 (5.7)	52.0 (6.3)	52.2 (6.8)	52.0 (7.0)	53.5 (6.8)	52.8 (6.9)
Min - Max	41–69	38–69	38–76	37–75	36–71	36–67
p-value*	0.7766		0.8205		0.5307	
Race n (%)						
White	49 (64.5)	49 (65.3)	53 (71.6)	58 (76.3)	54 (71.1)	55 (71.4)
Black (African heritage)	21 (27.6)	24 (32.0)	19 (25.7)	14 (18.4)	17 (22.4)	16 (20.8)
Asian	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	4 (5.3)	0 (0.0)	2 (2.7)	3 (3.9)	3 (3.9)	4 (5.2)
American Indian or Alaskan Native	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multi-racial	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.3)	2 (2.6)	1 (1.3)
Other	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
p-value*	0.1600		0.5884		1.0000	
Height (in)						
Mean (SD)	64.8 (2.8)	64.8 (2.1)	64.9 (2.8)	64.4 (2.3)	64.1 (2.5)	64.5 (2.6)
p-value*	0.9399		0.3179		0.4203	
Weight (lb)						
Mean (SD)	162.7 (29.9)	159.8 (29.3)	161.5 (28.8)	162.6 (27.2)	157.8 (25.2)	155.9 (25.1)
p-value*	0.5597		0.8188		0.6426	
BMI (kg/m^2)						
Mean (SD)	27.3 (4.8)	26.8 (4.2)	27.0 (4.6)	27.5 (4.5)	27.0 (4.1)	26.4 (4.0)
p-value*	0.4735		0.5023		0.3564	
Hot Flushes						
Mean (SD)	10.78 (3.58)	12.55 (11.94)	12.66 (7.33)	12.13 (6.10)	11.81 (4.07)	12.41 (5.59)
p-value*	0.3521		0.6265		0.6527	
Menopausal Status n (%)						
Surgical**	25 (32.9)	27 (36.0)	26 (35.1)	31 (40.8)	31 (40.8)	34 (44.2)
Natural ***	51 (67.1)	48 (64.0)	48 (64.9)	45 (59.2)	45 (59.2)	43 (55.8)

* Tests for treatment differences used ANOVA for continuous variables and Fisher's Exact test for categorical variables.
** Subjects with a bilateral oophorectomy were considered surgically postmenopausal.
*** Naturally menopausal subjects were considered to be any subject who had not undergone a bilateral oophorectomy.
SD = Standard Deviation; lb = pounds; in = inches

Note approximately 70% (318/545) of subjects were White, 24.4% (111/454) were Black, 3.5% (16/454) were Hispanic, 5 (1.1%) were multi-racial, and 1 each was either American Indian or Alaskan Native or Other. The mean age was 52.7± 6.4 years and subjects ranged in age from 36 to 76 years of age. The average BMI was 27.1± 4.5 kg/m^2 and there were no statistically significant difference between treatment groups. Also note the majority of subjects were naturally menopausal.

Reviewer's Comment
The race/ethnicity of randomized subjects roughly approximate the US population except for there being a greater number of Blacks compared to Hispanic subjects and a lesser number of Asian subjects than are seen in the current US population census.

Compliance
With the exception of the initial dose of study medication, which was administered at the site under supervision by the study staff, doses were administered by the subject at home without direct supervision. Compliance was assessed by a review of subject diaries and by querying the subject regarding the number of missed doses at each visit. A total of 73 subjects reported missing 1 or more doses during treatment, with the number of missed doses ranging from 1 (32 subjects) to 19 (1 subject).

In addition to the compliance data originating from subject diaries, an audit of returned supplies was conducted at the packaging facility [redacted], by VIVUS personnel upon completion of the study. During the audit, drug applicators from a random sample of 23 subjects, representing 5% of the overall drug supply, were disassembled. Residual volume was measured in these applicators and compared to the expected volume that would be predicted from each subject's diary records. In all cases, the measured volumes were within 20% of the volumes that would be predicted from the diary records, indicating that subject diary assessments of drug compliance provided a reasonably accurate representation of actual compliance during the trial

b(4)

Primary Efficacy Analyses
The following modified reviewer's tables (5-10) show the change from baseline in the mean number of moderate to severe hot flushes and the mean change in severity of hot flushes from baseline to week 12 (Study EST-01):

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Table 5: Change from Baseline in the Mean Number of MSVS 3 Sprays

Week	Frequency #3-Sprays Estradiol		#3-Sprays Placebo	
	Mean #of Hot Flushes (Number per day) N = 76	Mean Change from Baseline	Mean #of Hot Flushes (Number per day) N = 75	Mean Change from Baseline
0	**10.78**		**12.55**	
1	7.99	-2.79	9.52	-3.03
2	5.99	-4.39*	8.65	-3-90
3	5.19	-5.59*	7.90	-4.65
4	**4.14**	**-6.64****	**8.01**	**-4.54**
5	3.36	-7.32*	7.60	-4.95
6	3.06	-7.62*	7.58	-4.97
7	2.70	-7.98*	7.38	-5.17
8	2.62	-8.06*	7.18	-5.37
9	2.38	-8.30*	7.16	-5.39
10	2.20	-8.48*	7.13	-5.42
11	2.01	-8.67*	7.15	-5.40
12	**2.24**	**-8.44****	**7.23**	**-5.32**

**p<0.0002 at week 4; p <0.0001 at week 12

Test for pair wise differences (estradiol vs. placebo) between treatment groups of the same level using an ANCOVA where treatment, region and treatment by region interaction are included as factors and baseline score is the covariate

The following reviewer's tables shows the change from baseline in the mean weekly severity of moderate to severe hot flushes (MSVS) 3 sprays (Study EST-01)

Table 6: Mean Weekly Change from Baseline in Severity of MSVS-3-Sprays

Week	Severity-3-Sprays Estradiol		Placebo	
	Mean Weekly Severity- 3-sprays- N = 76	Mean Weekly Change-Severity	Mean Weekly Severity 3-sprays-Placebo- N = 75	Mean Weekly Change-Severity
0	**2.58**		**2.54**	
1	2.45	-0.13	2.46	-0.08
2	2.37	-0.21	2.44	-0.10
3	2.24	-0.34**	2.44	-0.10
4	**2.15**	**-0.43****	**2.41**	**-0.13**
5	1.95	-0.63**	2.36	-0.18
6	1.73	-0.85**	2.35	-0.19
7	1.67	-0.91**	2.34	-0.20
8	1.69	-0.89**	2.30	-0.24
9	1.57	-1.01**	2.30	-0.24
10	1.62	-0.96**	2.28	-0.26
11	1.47	-1.11**	2.28	-0.26
12	**1.51**	**-1.07****	**2.23**	**-0.31**

Sponsor's Modified Table 14.9.1.1

** p < 0.0031 at week 4; p < 0.001 at week 12

Severity Score = (number moderate x 2 + number severe x 3)/(number moderate + number severe)

Test for pairwise differences (estradiol vs. placebo) between treatment groups of the same level using an ANCOVA where treatment, region and treatment by region interaction are included as factors and baseline score is the covariate

Table 7: Change from Baseline in the Mean Number of MSVS-2 Sprays

Week	Frequency #2-Sprays Estradiol		#2 Sprays Placebo	
	Mean #of Hot Flushes (Number per day) N = 76	Mean Change from Baseline	Mean #of Hot Flushes (Number per day) N =75	Mean Change from Baseline
0	**12.66**		**12.13**	
1	8.25	-4.41	9.36	-2.77
2	6.73	-5.93*	8.12	-4.01
3	6.08	-6.58*	7.69	-4.44
4	**5.36**	**-7.30***	**7.39**	**-4.74**
5	4.76	7.90*	7.29	-4.84
6	4.38	-8.28*	6.82	-5.31
7	4.26	-8.40*	6.90	-5.23
8	4.19	-8.47*	6.65	-5.48
9	4.03	-8.63*	6.20	-5.93
10	4.11	-8.55*	6.22	-5.91
11	3.98	-8.68*	6.04	-6.09
12	**4.00**	**-8.66***	**5.94**	**-6.19**

Sponsor's Modified Table 14.9.1.2 received February 1, 2007
*p < 0.0027 at week 4; p < 0.0099 at week 12

Test for pairwise differences (estradiol vs. placebo) between treatment groups of the same level using an ANCOVA where treatment, region and treatment by region interaction are included as factors and baseline score is the covariate

The following reviewer's table 8 shows the change from baseline in the mean weekly severity of moderate to severe hot flushes 2 sprays (Study EST-01)

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Table 8: Mean Weekly Change from Baseline in Severity of MSVS 2-Sprays

Week	Severity2-Sprays Estradiol		2 Sprays Placebo	
	Mean Weekly Severity-2-sprays-N = 74	Mean Weekly Change-Severity	Mean Weekly Severity 2-sprays-Placebo-N = 76	Mean Weekly Change-Severity
0	**2.54**		**2.54**	
1	2.33	-0.21	2.42	-0.12
2	2.16	-0.38	2.31	-0.23
3	2.06	-0.48	2.29	-0.25
4	**1.97**	**-0.57****	**2.29**	**-0.25**
5	1.91	-0.63**	2.23	-0.31
6	1.85	-0.69**	2.15	-0.39
7	1.79	-0.75**	2.16	-0.38
8	1.78	-0.76**	2.12	-0.42
9	1.67	-0.87**	2.09	-0.45
10	1.66	-0.88**	2.06	0.48
11	1.67	0.87**	2.07	-0.47
12	**1.62**	**-0.92****	**2.00**	**-0.54**

Sponsor's Modified Table 14.9.1.2 received February 1, 2007
** $p < 0.0160$ at week 4; $p < 0.0406$ at week 12
Severity Score = (number moderate x 2 + number severe x 3)/(number moderate + number severe)

Table 9: Change from Baseline in the Mean Number of MSVS-1 Spray

Week	Frequency #1-Spray Estradiol		#1 Spray Placebo	
	Mean #of Hot Flushes (Number per day) N = 76	Mean Change from Baseline	Mean #of Hot Flushes (Number per day) N = 77	Mean Change from Baseline
0	**11.81**		**12.41**	
1	8.34	-3.47	10.12	-2.29
2	7.06	-4.75*	9.40	-3.01
3	6.26	-5.55*	9.08	-3.33
4	**5.55**	**-6.26***	**-8.77**	**-3.64**
5	5.05	-6.76*	8.70	-3.71
6	4.69	-7.12*	8.37	-4.04
7	4.39	-7.42*	8.15	-4.26
8	3.96	-7.85*	7.94	-4.47
9	3.96	-7.85*	8.11	-4.30
10	3.79	-8.02*	8.19	-4.22
11	3.74	-8.07*	7.90	-4.51
12	**3.71**	**-8.10***	**7.65**	**-4.76**

Sponsor's Modified Table 14.9.1.3 received February 1, 2007
*$p < 0.00010$ at week 4; $p < 0.0004$ at week 12
Test for pairwise differences (estradiol vs. placebo) between treatment groups of the same level using an ANCOVA where treatment, region and treatment by region interaction are included as factors and baseline score is the covariate

The following reviewer's table 10 shows the change from baseline in the mean weekly severity of moderate to severe hot flushes 1 spray (Study EST-01)

Table 10: Mean Weekly Change from Baseline in Severity of MSVS 1-Spray

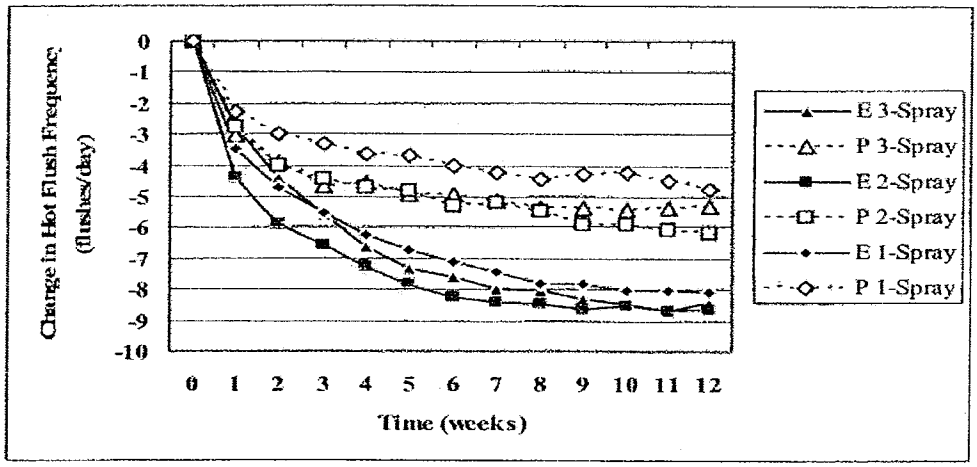
Week	Severity 1-Spray Estradiol		1 Spray Placebo	
	Mean Weekly Severity-1-sprays N = 76	Mean Weekly Change-Severity	Mean Weekly Severity 1-spray-Placebo- N = 77	Mean Weekly Change-Severity
0	**2.53**		**2.55**	
1	2.32	-0.21	2.41	-0.14
2	2.26	-0.27	2.38	-0.17
3	2.15	-0.38	2.39	-0.16
4	2.06	-0.47	2.36	-0.19
5	1.96	**-0.57****	2.38	-0.17
6	1.85	-0.68**	2.33	-0.22
7	1.79	-0.74**	2.33	-0.22
8	1.69	-0.84**	2.30	-0.25
9	1.62	-0.91**	2.30	-0.25
10	1.61	-0.92**	2.30	-0.25
11	1.55	-0.98**	2.30	-0.25
12	**1.49**	**-1.04****	**2.29**	**-0.26**

Sponsor's Modified Table 14.9.1.3 February 1, 2007
**At week 4 the p value is 0.0573; at week 12 p = <0.0001
Severity Score = (number moderate x 2 + number severe x 3)/(number moderate + number severe

A statistically significant ($p < 0.01$) reduction was observed in the frequency of moderate to severe hot flushes for all 3 estradiol dose levels at weeks 4 and 12. This reviewer notes that the significant change was observed beginning at week 2 for all doses and continued to week 12. Also noted from a *clinical viewpoint there is a greater than 2 hot flush difference per day* between estradiol and placebo for all doses at week 4 that was maintained throughout the study; the greatest difference was noted in the 2-spray dosage at week 4 and a greater difference between placebo and estradiol was noted at week 12 in the 1-spray dose. In reviewing mean change in severity of hot flushes this reviewer notes that the p-value for the 1-spray dose is 0.0573 at week 4 but becomes significant at week 5 and continues to be statistically significant to week 12 of treatment.

The following two figures (Figure 5: Change in Frequency of MSVS Over Time, ITT/Safety Population and Figure 6: Change in Severity Score of MSVS Over Time, ITT/Safety Population) demonstrate the change in frequency and severity of moderate to severe vasomotor symptoms over time in the ITT/Safety population. These figures closely mirror the previous 6 tables.

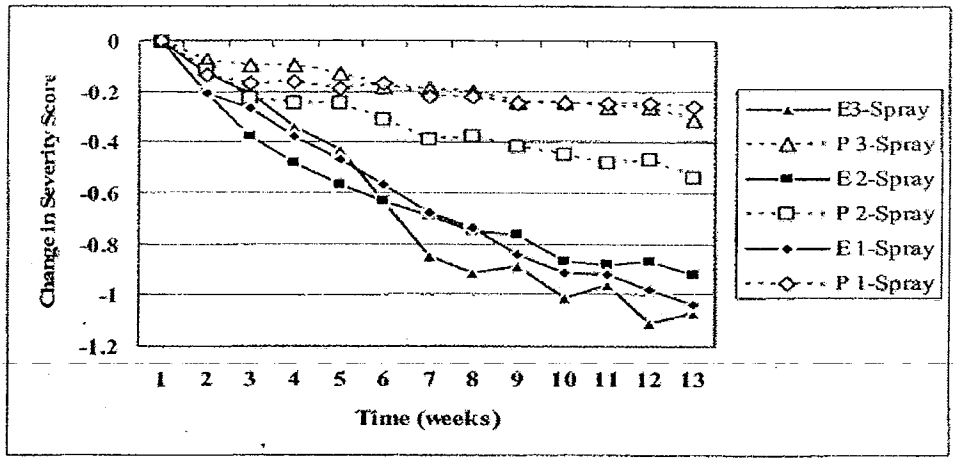
Figure 5: Change in Frequency of MSVS Over Time, ITT/Safety Population



Source: Section 14, Tables 14.9.1.1, 14.9.1.2, 14.9.1.3

All p values are statistically significant ($p < 0.05$) at week 2 in all dose groups. By week 4, the difference in hot flush frequency between estradiol and placebo exceeded *2 per day in all dose groups.*

Figure 6: Change in Severity Score of MSVS Over Time, ITT/Safety Population



A significant $p < 0.05$ reduction in hot flush severity score was initially achieved at weeks 3, 4, and 5 in the 3-, 2-, and 1-spray estradiol groups relative to placebo, respectively.

The sponsor also reported *in subgroup analyses* the frequency of hot flushes at Week 4 and Week 12 in subjects who were less than 50 years of age, subjects who were between the ages of 50-59 and subjects greater than 59 years of age, subjects who were surgically menopausal, naturally menopausal, subjects who with a BMI $<=25kg/m^2$, subjects with BMI $> 25kg-30g/m^2$, and subjects with BMI $>30kg/m^2$. Summations of the subgroup analyses show the following trends:

There were 140 subjects who were < 50 years of age. The age of subjects in the 3-spray, 2-spray and 1-spray treatment groups ranged from 18 to 27. At week 4 none of the subjects in the 3 spray group achieved the 0.05 significance level; at week 12, the 3-spray and the 1-spray achieved the p= 0.05 significance level (Table 14.7.1.4).

There were 259 subjects who ranged in age between of 50 and 59. The age of subjects in the 3-spray, 2-spray and 1-spray treatment groups ranged from age 38 to 47. At week 4 all three treatment groups had achieved the p = 0.05 significance level. At week 12, the 3-spray and the 1-spray doses maintained the p= 0.05 significance level while the 2-spray dose showed a positive statistical trend of p = 0.0574 (Table 14.7.1.5).

There were 57 subjects who age was > 59 years. The number of subjects in the 3-spray, 2-spray and 1-spray treatment groups ranged from 5 to 12. At week 4 none of the treatment groups achieved a p =0.05 significance level; at week 12, the 3-spray and the 1-spray dosages maintained a p = 0.05 significance level (Table 14.7.1.6).

The number of subjects who were White totaled 318. The number of subjects ranged from 49 to 58 years of age in the 3-spray, 2-spray, and 1-spray treatment groups. At weeks 4 and 12 all three treatment group achieved the p = 0.05 significance level (Table 14.7.1.7).

The number of subjects in the not White group totaled 136. The number of subjects ranged from 18 to 27 in the 3-spray, 2-spray and 1-spray treatment groups. At week 4 none of the 3 sprays achieved the p=0.05 level. At week 12, only the 3-spray treatment group achieved the p= 0.05 significance level (Table 14.7.1.8).

The number of subjects who were surgically menopausal was 174. The number of subjects ranged from 25 to 34.in the 3-spray, 2-spray and 1-spray treatment groups. At week 4 the 2-spray dose achieved a p=0.05 significance level. At 12 weeks all three treatment group achieved a p = 0.05 significance level (Table 14.7.1.9).

The number of subjects in the naturally menopausal group was 280. The number of subjects ranged from 43 to 51 in the 3-spray, 2-spray and 1-spray treatment groups. At weeks 4 and 12 the 3-spray and the 1-spray doses achieved the p 0.05 significance level. The 2-spray dose did not achieve statistical significance at either week 4 or 12.

The number of subjects with a BMI <=25kg/m^2 totaled 180. The number of subjects in the 3-spray, 2-spray and 1-spray treatment groups ranged from 24 to 36. The 1-spray dose achieved a p =0.05 significance at week 4. At week 12 the 3-spray and the 1-spray doses achieved the p=0.05 significance level (Table 14.7.1.11).

The number of subjects with a BMI > 25kg-30g/m^2 totaled 160. The number of subjects in the 3-spray, 2-spray and 1-spray treatment groups ranged from 23 to 32. At week 4 and 12 all three doses achieved a significance level of p =0.05(Table 14.7.1.12).

The number of subjects with a BMI > 30kg/m^2 totaled 114. The number of subjects in the 3-spray, 2-spray and 1-spray treatment groups ranged from 16 to 23. At week 4 none of the treatment groups achieved a significance level of p=0.05. At week 12 the 1-spray dose achieved a significance level of p < 0.05(Table 14.7.1.13).

Reviewer's Comment
Surgical status at menopause, age less than 50 and BMI are known parameters that impact upon the overall efficacy of subjects who are receiving hormonal therapy. Subgroup analyses were not powered to assess primary endpoint differences in any subgroup; the results from the subgroups analyzed do not demonstrate reproducibly statistically significant differences between treatment and placebo.

Secondary Endpoints
Addition of mild symptoms to severity score
Similar efficacy results were obtained when the sponsor reported on the number of mild (1) = moderate x 2= number severe x3/total number of hot flushes as compared to moderate to severe symptoms. For the 3-spray dose statistical significance was observed at week 4, p = 0.0014 for frequency and at week 3 for severity. Clinically, the difference in hot flushes frequency was 1.40 hot flushes per day; statistical significance was observed with a p value < 0.001 from week 5 through week 12 for the 3-spray dose. For the 2-spray dose statistical significance was observed at *week 1* for frequency at week 3 for severity. A statistical reduction was observed in all remaining weeks of treatment after the initial reduction in frequency and severity at week 1 for frequency and at week 3 for severity. From a clinical viewpoint, there was a reduction in the frequency of hot flushes of 2.09 hot flushes per day at week 1in the 2-spray dose. A statistical reduction was observed in all remaining weeks of treatment after the initial reduction in frequency (week 1) and severity (week 3). For the 1-spray dose statistical significance was observed at week 3 for frequency and at week 4 for severity. A statistical reduction was observed in all remaining weeks of treatment after the initial reduction in frequency in frequency and severity at week 3 for frequency and week 4 for severity. From a clinical viewpoint, the reduction of hot flushes was 2.31 hot flushes per day at week 3

The sponsor reported *in post hoc analyses in subjects who were* 90% and 75% responders. A 90% or greater reduction in the frequency of vasomotor symptoms was observed at week 4 in 11 (14.5%), 18 (24.3%) and 11 (14.5%) in subjects in the 3-, 2-, and 1-spray estradiol groups compared to 5 (6.7%) 9 (11.8%) and 5 (6.5%) of placebo subjects; at week 12 a reduction in vasomotor symptoms of 36 (47.4%), 29 (39.2%) and 33 (43.4%) was observed in the 3-, 2-, and 1-spray estradiol groups respectively, compared to 12(16.0%), 19 (25.0%), and 10 (13.0%) was observed in the 3-, 2-, and 1-spray placebo groups For severity, between 21.6% and 25% of estradiol subjects and 3.9%-13.2% of placebo subjects exhibited a 90% reduction or greater response at week 12.

A 75% responder or greater reduction in the frequency of vasomotor symptoms was observed at week 4 in 30 (39.5%), 26 (35.1%), and 21 (27.6%) in subjects in the 3-, 2-, and 1-spray estradiol groups compared to 12 (16%), 16 (21.1%), and 12 (15.6%) of placebo subjects. At week 12 a reduction in vasomotor symptoms of 50 (65.8), 39 (52.7%) and 49 (59.2%) was observed in the

3-, 2-, and 1-spray estradiol groups compared to 19 (25.3%), 26 (34.2%) and 19 (24.7%) in the 3-, 2-, and 1-spray placebo groups

In the per protocol analyses 50% responders were analyzed. At week 4 a reduction in moderate to severe vasomotor symptoms was observed in 52 (68.4%), 43 (58.1%) and 41 (53.9%) in subjects in the 3-, 2-, and 1-spray estradiol groups compared to 29 (38.7%, 28 (36.8%) and 21 (27.3%) of placebo subjects. At week 12, 65 (85.5%), 55 (74.3%) and 58 (76.3%) was observed in the 3-, 2-, and 1-spray estradiol groups compared to 33 (44.0%), 40 (52.6%) and 32 (41.6%) of placebo subjects.

Reviewer's Comment
These responder analyses, whether per protocol or post hoc provide useful information in a small segment of women. At week 12, which is not the most important primary endpoint, a variable percentage of subjects will show some improvement in the reduction of vasomotor symptoms in both frequency and severity. *No dose response effect* was evident for the 50%, 75% and 90% responder analyses for either vasomotor symptom of frequency or severity. For all three analyses, subjects appeared to achieve a 50%, 75% or 90% responder level more rapidly for frequency than was observed for severity.

The Greene Climacteric Scale was employed to assess the effect of treatment on climacteric symptoms. Differences were observed between the estradiol and placebo treated populations in the vasomotor domain (questions 19 and 20) and for the individual questions from that domain. Across all estradiol treatment groups, subjects reported significant reduction in vasomotor symptom scores ($p< 0.003$), night sweat scores ($p< 0.003$) and hot flush score ($p< 0.02$) relative to placebo.

Global Assessment
At completion of the study 64.5% of subjects treated with 3 sprays of estradiol reported marked improvement of vasomotor symptoms compared to 21.3% of subjects treated with placebo ($p<0.001$). Similar results were observed at all dose levels although the proportion of subjects reporting marked improvement on treatment appeared somewhat higher 64.5% in the 3-spray estradiol group compared to the 2-spray and 1-spray groups (43.2% and 46.4%, respectively.

Clinical **Microbiology**
No anti-microbiology studies were performed with this submission.

6.1.5 Efficacy Conclusions

The 3-spray and the 2-spray dosages were statistically significantly different from placebo at week 4 and 12 in the treatment of moderate to severe vasomotor symptoms. A positive treatment effect was observed at week 2 to 3 and this treatment effect continued through week 12. The 1-spray dose was statistically significant different from placebo at week 4 for frequency but not for severity of symptoms. Severity of symptoms was statistically significantly different from placebo at week 5 and this continued through week 12.

7 INTEGRATED REVIEW OF SAFETY

The safety of Evamist™ is supported by one study (EST-01). Criteria used to assess the safety of Evamist™ were: adverse events, vital signs, physical examinations, transvaginal ultrasound, mammogram and clinical laboratory test. Approximately 458 subjects were randomized into treatment, 454 received at least one dose of test material and were analyzed for safety in the intent-to-treat population. The duration of exposure for the 3-spray dose estradiol was 85.7± 18.2 days and 74.1 ± 28.6 days for placebo; for the 2 spray dose estradiol the duration of exposure was 78.3 ± 21.8 days and 79.0 ± 21.5 days for placebo; for the 1-spray estradiol the duration of exposure was 83.1 ± 21.5days and 75.9 ± 27.2 days for placebo.

Subjects with an intact uterus were required per protocol to take medroxyprogesterone acetate (MPA) 5mg or 10 mg per day for 2 weeks following the completion of treatment to mitigate any possible increased risk of endometrial hyperplasia resulting from unopposed estrogen therapy. Overall, 75 (33.2%) estradiol treatment subject and 78 (34.2%) placebo subjects received MPA therapy.

7.1 Methods and Findings

The overall frequency of AEs is summarized in the following table:

Table 11: Overall Adverse Events

	3-Sprays		2-Sprays		1-Spray	
	Estradiol N = 76	Placebo N= 75	Estradiol N =74	Placebo N = 76	Estradiol N = 76	Placebo N= 77
Subjects with at least 1 treatment-emergent AE n (%)	46 (60.5)	38 (50.7)	41 (55.4)	41 (53.9)	42 (55.3)	35 (45.5)
Subjects with at least 1AE related to treatment* n (%)	32 (42)	21 (28)	26 (35)	26 (34)	30 (39)	14 (18)
Subjects discontinued due to treatment-emergent AE n (%)	2 (2.6(	1 (1.3)	2 (2.6)	3 (3.9)	2 (2.6)	2 (2.6)
Subjects discontinued due to AE related to treatment* n (%)	2 (2.6)	1 (1.3)	2 (2.6)	1 (1.3)	1 (1.3)	1 (1.3
Subjects with at least 1 treatment-emergent serious AE N (%)	3 (3.9)	0 (0.0)	1 (1.4)	0 (0.0)	3 (3.9)	1 (1.3
Subjects deaths n (%)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0	0 (0.0	0 (0.0

*For purposes of this report, an adverse event was considered to be related to treatment if its relationship was assessed as "related", probably related", possibly related" or probably not" related.

Reviewer's Comment
Note than 12 subjects withdrew from the study, 6 in the estradiol treatment group and 6 in the placebo groups. In the estradiol groups, 5 subjects were withdrawn due to adverse events considered related to treatment (ovarian cyst, headache, nipple pain, chest pain and nausea). Three placebo subjects withdrew due to treatment-related events (increased blood pressure, pruritic rash, vaginal hemorrhage).

7.1.1 Deaths

There were *no* deaths in the clinical trial.

7.1.2 Other Serious Adverse Events

Nine (9) treatment-emergent serious adverse events were reported in 8 subjects (7, estradiol; 1, placebo). Of this total, events in 3 subjects (37.5%) were classified as not related to treatment; in 5 subjects (62.5%) the events were considered probably not related. During the screening period a case of adenocarcinoma of the breast was identified prior to randomization and treatment.

Table 12: Summary of Serious Adverse Events

Subject	Age	Treatment Group	MedDRA Term	Duration	Relationship To Treatment	Severity	Outcome
6280134	62	E 1-Spray	Dyspnea	1 day	Probably not	Severe	Resolved
6360107	71	E 1-Spray	COPD exacerbated	1 day	Probably not	Mild	With Sequelae
6450126*	42	E 1-spray	Uterine prolapse	1 day	Not related	Moderate	Resolved
6050104	51	E 2-Spray	Spinal Column Stenosis	7 Days	Not related	Severe	Resolved
6110109	52	E 3-Spray	COPD exacerbated	3 days	Not related	Severe	Resolved
6280111	43	E 3 Spray	Impaired Gastric Emptying	1 day	Probably not	Severe	Resolved
6550127	55	E 3-Spray	Chest pain	1 day	Probably not	Severe	Resolved
6420116	39	P 1-spray	Palpitations	4 days	Probably not	Moderate	Resolved
6420116	39	P 1-Spray	Dizziness	4 days	Probably not	moderate	Resolved
6550131**	55	Not Randomized	Breast Cancer	2 days	Not related	Severe	With Sequelae

Table modified from Sponsor's Table 22, Volume 29
*Subject discontinued due to event
** Adenocarcinoma of left breast identified during Screening. Subject withdrawn prior to randomization and is not listed in Listing

7.1.3 Dropouts and Other Significant Adverse Events

The following table shows subjects who discontinued from treatment due to a treatment-emergent adverse event (TEAE):

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Table 13: TEAEs Resulting in Subject Discontinuation from Treatment *

Subject	Age	Treatment Group	MedDRA Term	Duration	Relationship to Treatment	Severity	Outcome
6430141	49	E 1-spray	Ovarian Cyst	19 days	Possibly	Severe	Resolved
6450126#	42	E 1-Spray	Uterine Prolapse	1 day	Not Related	Moderate	Resolved
6430148	42	E 2-Spray	Headache	17 days	Possibly	Severe	Resolved
6430150	54	E 2-Spray	Nipple Pain	1 day	Possibly	Moderate	Resolved
6450142	52	E 3-Spray	Chest Pain	1 day	Probably Not	Moderate	Resolved
6430143	57	E 3-Spray	Nausea	20 days	Possibly	Moderate	Resolved
6320113	48	P 1-Spray	Increased Blood Pressure	10 days	Not Related	Moderate	Continuing
380129	58	P-1 Spray	Anxiety	1 Day	Not Related	Moderate	Continuing
			Depression	1 day	Not Related	Moderate	Continuing
6070106	40	P 2-Spray	Computerized CAT Scan Abnormal	1 day	Not Related	Mild	Continuing
6180113	51	P 2-Spray	Pruritic Rash	7 Days	Related	Moderate	Resolved
6430120**	51	P 2-Spray	Rectal Perforation	July 05	Not Related	Unknown**	Unknown
			VulvovaginalDryness	July 05	Not Related	Unknown**	Unknown
			Bladder Pain	July 05	Not Related	Unknown**	Unknown
			Constipation	July 05	Not Related	Unknown**	Unknown
6430130	50	P 3-Spray	Vaginal Hemorrhage	7 Days	Probably	Moderate	Resolved

Modified from sponsor's table 23, Vol. 29
*The reason for discontinuation was remapped to adverse event from request to withdraw, intercurrent illness or other more closely fit underlying cause for discontinuation.
#Serious Adverse Event. Subject also report in previous table
**Subject lost to follow=up. Subject reported adverse event after last visit to study site.

Reviewer's Comment
Note there is very little correlation between subjects with serious adverse events and subjects who discontinued from the study due to a TEAE. Also note equal number of subjects discontinued in the treatment groups and the placebo groups

7.1.3.1 Overall profile of dropouts

Note equal number of subjects discontinued in the treatment groups and the placebo groups. Note that most subjects in the estradiol groups had TEAEs that are consistent with estrogen therapy; note that in the placebo groups there is a wide range of TEAEs that have no correlation with estrogen effects. Subject 6430120 had a myriad of TEAEs and were lost to follow-up, these TEAEs are not related to the study drug

7.1.3.2 Adverse events associated with dropouts

Five of 6 TEAEs are possibly related to estrogen therapy with the outlier being uterine prolapse which is more associated with poor tensile strength in the vaginal wall. The subject with chest pain (6050142) received the therapy for one day and was discontinued as was subject 6450126 who developed uterine prolapse. Cause and effect are clearly debatable in these 2 subjects. Four 4 subjects (6430141, 6430148, 6430150, 6430143) took estrogen therapy for greater than 10 days, while subject 6050142 complained of chest pain and was discontinued on day 1.

7.1.3.3 Other significant adverse events

There are no "Other Significant Adverse Events" associated with this study.

7.1.4 Other Search Strategies

There are no special searches in pivotal trial EST-01.

7.1.4.1 Eliciting adverse events data in the development program

After randomization, subjects were seen every 4 weeks until week 12 ±1 week; a post treatment visit was scheduled at week 16-18 (±1) weeks.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse events in study EST-01 were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 1.The total number of subjects reporting treatment-emergent events was summarized for each treatment (within each group) by system organ class and by preferred term. In addition, each adverse event was summarized by severity and relationship to study drug. If more than one adverse event was mapped to the same preferred term, it was counted once per subject using the event with the highest severity and closest relationship to study drug. All adverse event analyses were performed on the ITT/safety population.

7.1.4.3 Incidence of common adverse events

TEAEs of any severity were reported in 243 subjects (53.3%); adverse events were reported in 129 (57.1%) of subjects treated with estradiol and 114 (50%) placebo subjects. TEAEs with a reporting frequency of at least 1% of all subjects treated in the study (i.e. at least 5 subjects, regardless of treatment group) were summarized in Sponsor's table 16, Vol. 29. Table 29 will now be summarized. Headache was the most frequent reported adverse event, with 40 subjects (8.8%) reporting one or more headaches during the study. Headaches were reported in 24 (10.6%) of estradiol treated subjects (8 in the 3-spray; 9, 2-spray; 7. 1-spray). Among the placebo subjects, 16 (7.0%) of subjects reported 1 or more headaches (7 in the 3-spray; 5, 2-spray; 4, 1-spray). Breast tenderness was reported in 17 subjects, 13 estradiol (5.5%) and 4 placebo (1.8%). Metrorrhagia was reported in 9 subjects (2.0%), 7 (3.1%) estradiol treatment and 2 (0.9%) placebos. Nausea, back pain, nasopharynitis and arthralgia were reported in 15 (3.3%),

12 (2.6%) and 10 (2.2%) of subjects, respectively. No dose response was evident due to the limited number of subjects reporting in each treatment group.

TEAEs were reported somewhat more frequently in subjects 50-59 years of age in the estradiol groups (63.4%) although placebo subjects 50-59 years of age had similar adverse event rate (49.2%) to the overall placebo rate; slightly more estradiol-treatment subjects in the 50-59year age range (17.2%) reported headache.

7.1.4.4 Common adverse event table reported at greater than 1% (Sponsor's table 16, Vol.29

Table 14: Common adverse tables

Event	Frequency n (%)					
	3 Sprays		2 Sprays		1 Spray	
	Estradiol (N = 76)	Placebo (N = 75)	Estradiol (N = 74)	Placebo (N = 76)	Estradiol (N = 76)	Placebo (N = 77)
Infections and Infestations						
Nasopharyngitis	1 (1.3)	1 (1.3)	3 (4.1)	2 (2.6)	4 (5.3)	1 (1.3)
Sinusitis	2 (2.6)	2 (2.7)	2 (2.7)	0 (0.0)	2 (2.6)	1 (1.3)
Urinary Tract Infection	1 (1.3)	1 (1.3)	3 (4.1)	2 (2.6)	1 (1.3)	1 (1.3)
Upper Respiratory Tract Infection	2 (2.6)	0 (0.0)	0 (0.0)	2 (2.6)	1 (1.3)	1 (1.3)
Influenza	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.3)
Vaginitis Bacterial	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.3)	1 (1.3)	2 (2.6)
Nervous System Disorders						
Headache	8 (10.5)	7 (9.3)	9 (12.2)	5 (6.6)	7 (9.2)	4 (5.2)
Dizziness	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.3)	2 (2.6)	1 (1.3)
Reproductive System and Breast Disorders						
Breast Tenderness	4 (5.3)	0 (0.0)	5 (6.8)	4 (5.3)	4 (5.3)	0 (0.0)
Metrorrhagia	3 (3.9)	1 (1.3)	2 (2.7)	1 (1.3)	2 (2.6)	0 (0.0)
Nipple Pain	1 (1.3)	0 (0.0)	5 (6.8)	0 (0.0)	2 (2.6)	0 (0.0)
Vaginal Hemorrhage	2 (2.6)	2 (2.7)	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.3)
Breast Discoloration	2 (2.6)	0 (0.0)	1 (1.4)	0 (0.0)	2 (2.6)	0 (0.0)
Breast Pain	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.3)	1 (1.3)	1 (1.3)
Gastrointestinal Disorders						
Nausea	2 (2.6)	4 (5.3)	2 (2.7)	1 (1.3)	1 (1.3)	5 (6.5)
Diarrhea	2 (2.6)	0 (0.0)	1 (1.4)	2 (2.6)	0 (0.0)	2 (2.6)
Dyspepsia	2 (2.6)	1 (1.3)	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.3)
Musculoskeletal and Connective Tissue Disorders						
Back Pain	2 (2.6)	1 (1.3)	4 (5.4)	2 (2.6)	2 (2.6)	1 (1.3)
Arthralgia	3 (3.9)	0 (0.0)	1 (1.4)	4 (5.3)	1 (1.3)	1 (1.3)
Pain in Extremity	2 (2.6)	1 (1.3)	1 (1.4)	1 (1.3)	1 (1.3)	0 (0.0)
Investigations						
Smear Cervix Abnormal	2 (2.6)	0 (0.0)	1 (1.4)	1 (1.3)	0 (0.0)	2 (2.6)
GGT Increased	2 (2.6)	0 (0.0)	2 (2.7)	1 (1.3)	0 (0.0)	0 (0.0)
General Disorders and Administrative Site Conditions						
Fatigue	0 (0.0)	0 (0.0)	2 (2.7)	2 (2.6)	1 (1.3)	1 (1.3)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.3)	1 (1.3)	1 (1.3)
Psychiatric Disorders						
Insomnia	0 (0.0)	1 (1.3)	1 (1.4)	3 (3.9)	1 (1.3)	2 (2.6)
Depression	0 (0.0)	2 (2.7)	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.3)
Vascular Disorders						
Hypertension	2 (2.6)	2 (2.7)	1 (1.4)	1 (1.3)	0 (0.0)	0 (0.0)
Immune System Disorders						
Seasonal Allergy	1 (1.3)	0 (0.0)	1 (1.4)	2 (2.6)	1 (1.3)	0 (0.0)

7.1.4.5 Identifying common and drug-related adverse events

Common and drug related adverse and drug related adverse events have been previously identified in this safety section. Important symptoms demonstrated in this study and estrogen studies in general include headache, nasopharynitis, breast pain, breast discomfort and tenderness, nausea, back pain, and hemorrhage.

7.1.4.6 Additional analyses and explorations

There are no additional analyses to be reported in this study.

7.1.5 Less Common Adverse Events

All adverse events are recorded that occurred at a greater than 1% incidence is shown in table 14 (Sponsor's table 16). Importantly, a single subject (#6340101) in the 2-spray estradiol group exhibited *simple hyperplasia without atypia on biopsy at the end of treatment*. The subject was given MPA (10mg and 20mg courses) following the end of treatment. A follow-up biopsy performed about 6 months after treatment was reported by the site as *atrophic*.

The following table shows endometrial biopsy results from baseline to the end of the study:

Table 15: Results of Endometrial Biopsies from Baseline to End-Of-Study

Score assigned to Visit	3- Spray Estradiol N = 76	3-Spray Placebo N = 76	2-Spray Estradiol N = 76	2-Spray Placebo N = 76	1-Spray Estradiol N = 77	1-Spray Placebo N = 77
Screening (VI)						
N	31	37	23	28	26	28
0-No Sample	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1 Insufficient	0 (0.0%)	1 (2.7%)	1 (4.3%)	0 (0.0%)	1 (3.8%)	1 (3.6%)
2 Atrophic	26 (83.9%)	30 (81.1%)	17 (73.9%)	26 (92.9%)	22 (84.6%)	22 (78.6%)
3 Inactive	4 (12.9%)	3 (8.1%)	1 (4.3%)	0 (0.0%)	2 (7.7%)	2 (7.1%)
4 Proliferative	1 (3.2%)	3 (8.1%)	3 (13.0%)	2 (7.1%)	1 (3.8%)	3 (10.7%)
5 Secretory	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6 Menstrual	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
7Simple Hyperplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
End of Week 12/Early Exit (V5)						
N	30	27	20	25	25	19
0-No Sample	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
1 Insufficient	4 (13.3%)	6 (22.2%)	0 (0.0%)	2 (8.0%)	1 (4.0%	3 (15.8%)
2 Atrophic	7 (23.3%)	16 (59.3%)	8 (40.0%)	19 (76.0%)	14 (56%)	12 (63.2%)
3 Inactive	13 (43.3%)	3 (11.1%)	4 (20.0%)	1 (4.0%)	5 (20.0%)	1 (5.3%)
4 Proliferative	6 (20.0%)	1 (3.7%)	6 (30.0%)	3 (12.0%)	4 (16.0%)	3 (15.8%)
5 Secretory	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6 Menstrual	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
7Simple Hyperplasia	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Modified from Sponsor's supplemental table July 2007

As stated in the previous paragraph there was one case of endometrial hyperplasia in the 2-spray dosage; at the end of 12 weeks of treatment there is increased endometrial proliferation from baseline in all three doses at 12 weeks of treatment.

7.1.6 Laboratory Findings

Vital Signs and Physical Examination
There were no notable changes in either blood pressure (systolic and diastolic) pulse or body weight from baseline.

Clinical laboratory abnormalities were infrequently reported as adverse event and were generally unrelated to treatment. Elevated gamma glutamyl transferase (GGT) or elevated hepatic enzymes (ALT and GGT) was the laboratory change most commonly reported as an adverse event (5, estradiol; 1, placebo). Subject 6440109 (1-spray estradiol) had baseline and end of treatment INR of 0.87 and 1.61, respectively; baseline and end of treatment prothrombin time was 10.4 and 19.3 seconds, respectively.

A total of 20 TEAEs of the skin and subcutaneous tissues and application site reaction were reported in 16 estradiol subjects; 20 TEAEs were reported in 19 placebo subjects. Of these 40 TEAEs the majority (77.5%) were not associated with the application site. In the estradiol treatment subjects, 6 events (1, 3-spray; 1, 2-spray, 4, 1-spray) were classified as related to treatment; 8 events in placebo subjects (6, 3-spray; 2, 2-spray) were considered to be treatment related. The most frequently reported event was contact dermatitis (1, estradiol; 1, placebo), all classified as unrelated to treatment. Rash was reported in 2 estradiol treatment and 2 placebo subjects; pruritic rash was reported in 1 estradiol-treatment and 2 placebo subjects; erythema was reported in 2 estradiol treatment and 1 placebo subject; in estradiol treatment subjects, a single instance of vulvar redness and papular rash was considered treatment related.

Adverse events related to treatment at the application site totaled 7(1.5%). Treatment related application site events were reported in 3 estradiol subjects (1, 3spray; 2, 1-spray). Subject [6180123, (1-spray)] had a severe itchy rash with scattered blisters. The other two estradiol subjects reported rash or skin irritation. In the 4 placebo treated subjects pruritic rash, rash, application site discomfort and application site erythema were reported. No action was taken with regard to study drug in 5 subjects. Placebo subject (6180113) was withdrawn from the trial as a result of the pruritic rash at the application site. Subject (6220107) received medication in treatment of application site erythema.

7.1.6.1 Overview of laboratory testing in the development program

All subjects who were exposed to at least one dose of trial medication were included in the safety analyses. A total of 454 subjects were evaluated Approximately 151 subjects received 3-sprays [estradiol (76), placebo (75)]; 150 received 2-sprays [estradiol (74) placebo (76)]; 153 received 1-spray [estradiol (76), placebo (77)].

7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory values are consistent with a placebo controlled trial and provide no new or additional safety signal.

7.1.6.3 Standard analyses and explorations of laboratory data

The standard analyses used in this study utilized the subjects age (> or <) the unit, lower and upper limits, material and the method used to analyzed the detection method. Analyses and exploration of laboratory data revealed no unusual SAEs/AEs.

7.1.6.3.1 Analyses focused on measures of central tendency

The sponsor provided most analyses using mean changes. Emphasis was placed on hematology changes, urinalysis, clinical chemistry, coagulation parameters and lipid profile.

7.1.6.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no additional analyzes that focused on outliers or shifts from the normal to abnormal. Specific numbers of subjects were outliers to reference range; overall, abnormal values in this study were not significant.

7.1.6.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no subjects who were discontinued from the study because of abnormal laboratory values.

7.1.6.4 Additional analyses and explorations

No additional analyses or explorations are required based upon the present data.

7.1.6.5 Special assessments

No special assessments were performed in this study.

7.1.7 Vital Signs

No special vital signs were obtained other than the usual blood pressure, pulse, body weight, etc.

7.1.7.1 Overview of vital signs testing in the development program

No special vital signs were obtained other than the usual blood pressure, pulse, body weight, etc. Vital signs were taken at each of the 6 visits including the exit visit.

7.1.7.2 Selection of studies and analyses for overall drug-control comparisons

This was a single study that included no drug-control comparisons.

7.1.7.3 Standard analyses and explorations of vital signs data

There were no standard analyses or explorations that focused on vital sign data.

7.1.7.3.1 Analyses focused on measures of central tendencies

There were no analyses that focused on measures of central tendency.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no analyses focused on outliers or shifts from normal to abnormal.

7.1.7.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no marked outliers, dropouts or vital sign abnormalities. One subject (placebo group) was withdrawn from the study due to an elevated blood pressure.

7.1.7.4 Additional analyses and explorations

There were no other additional analyses or explorations.

7.1.8 Electrocardiograms (ECGs)

There were no ECGs performed in this study.

7.1.8.1 Overview of ECG testing in the development program, including brief review of preclinical results

This study did not provide for any ECG testing (see Schedule of Events table)

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

There were no additional studies or analyses for overall drug control other than a small sample of the used devices that correlated the expected drug delivery based upon the number of sprays a subject would use and what remained in the device after it had been returned to the investigator.

7.1.8.3 Standard analyses and explorations of ECG data

This study did not provide for standard ECG testing.

7.1.8.3.1 Analyses focused on measures of central tendency

No analyses were performed since there was no ECG testing.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

No analyses were performed since there was no ECG testing.

7.1.8.3.3 Marked outliers and dropouts for ECG abnormalities

No analyses were performed since there was no ECG testing.

7.1.8.4 Additional analyses and explorations

No analyses were performed since there was no ECG testing

7.1.9 Immunogenicity

There was no special immunogenicity studies performed with this product.

7.1.10 Human Carcinogenicity

There was no special human carcinogenicity studies performed with this product.

7.1.11 Special Safety Studies

Special safety studies were performed regarding hemostatic parameters, lipids and the effect of estradiol sex hormone binding globulin (SHBG). The sponsor hemostatic parameters focused on antithrombin (AT-III), fibrinogen, INR, Protein C (%), Protein Activity (%) and Prothrombin time. Coagulation parameters at baseline and at the end of treatment were summarized in the ITT/Safety population in Table 24. Results will now be summarized for the 3-spray, 2-spray and 1-spray groups:

- Mean AT-III levels decreased by -9.4% ± 16%, -6.3% ± 13% and -8.2% ±10% in the 3-, 2-, and 1-spray groups, respectively. Mean AT-III levels decreases of -1.8% ±13), -3.7 ±19%, and -3.0 ±12% were seen in the 3-spray, 2-spray and 1-spray groups, respectively. Overall, it appears there is a modest estradiol related effect on AT-III.
- At the end of treatment mean fibrinogen levels decreased -31.4 ± 65 mg/dL in the 3-spray estradiol group compared to -15.7 ± 60mg/dL in 3-spray placebo subjects. Changes of -23.0 ±.47 mg/dL and -17.5 ±60mg/dL in the 2 spray and 1spray estradiol groups, respectively, were similar to those observed in placebo (-19.9 ± 66mg/dL and -16.6 ± 52mg/dL, respectively). The decreased fibrinogen level in the 3-spray estradiol group is unusual and may due to chance.
- Between screening and the end of treatment Protein S, Protein C and INR, the mean changes in serum levels were similar across treatment groups. There was no evidence of a treatment related effect.
- Prothrombin times for most subjects remained in the normal range throughout the study. Mean prothrombin times were slightly increased at the end of treatment (.03± 3.80 seconds, 1.9 ± 13.28 seconds) in all treatment groups except the 3-spray estradiol group (0.2 ± 2.24 seconds). These slight differences were not clinically relevant.
- Eleven subjects were screened for Factor V Leiden mutation (R506Q). All were heterozygous for this mutation. Coagulation parameters for these subjects were unremarkable, and none of these subjects had adverse events associated with possible increased coagulability.

Reviewer's Comment
Overall, there are no clinically significant changes in hemostatic parameters in this study.

- Lipid profiles were recorded at screening and at the end of treatment in the ITT/Safety population (Table 25, Vol. 30) Cholesterol levels decreased by -7.8±41, -6.3 ±22, and -8.3±24 mg/dL in the 3-,2-, and 1 spray treatment groups, respectively; in placebo subjects, cholesterol levels decreased by 5.1. ±24, 1.9 ±31 and -5.1±33 mg/dL 3-, 2-, and 1 spray treatment groups. Changes were similar in the estradiol and placebo groups and there was no apparent dose response effect.
- Mean high density lipoprotein (HDL) levels were in the normal range in all treatment groups at both baseline and end of treatment. Change from screening in the estradiol treatment groups (-1.2 ±7mg/dL, -2.0± 8mg/dL-3.1±7mg/dl for the 3-, 2-, and 1-spray groups, respectively were similar to those observed in the placebo groups (-2.9 ± 6mg/dL,-2.1 ±7mg/dL, -1.2 ±7mg/dL in the 3-, 2-, and 1-spray groups).
- Mean low density lipoprotein (LDL) was elevated throughout the study with a mean screening levels being somewhat higher than end of treatment. Changes from screening in the estradiol treatment groups (-9.6 ±24mg/dL, -9.0± 23mg/dL, 8.0±19mg/dL) for the 3-, 2-, and 1-spray groups, respectively) were similar to the changes in the 3-, 2-, and 1-spray placebo groups (-4.6 ±20mg/dL, -5.6± 26mg/dL, -8.3± 30mg/dL, respectively). For the vast majority of subjects, results remained either elevated or in the normal range throughout the study period.
- Mean lipoprotein (a) levels were slightly elevated at screening and at eh end of treatment in all study groups with the exception of the 1-spray group where high normal levels were reported.
- Normal triglycerides were reported in the majority of subjects at screening and the end of treatment; the mean triglyceride levels were in the normal range throughout the study. The magnitude of change between screening and the end of treatment was variable. In estradiol treatment subjects, triglyceride increased of 13.3± 66, 6.0 ± 49, and 7.2 ± 54mg/dL were observed in the 3-, 2-, 1-spray groups; changes of 3.3 ± 83, 26.3 ±78, and 4.2 ± 5.6mg/dL were reported in the 3-, 2-, 1-spray placebo groups, respectively

Reviewer's Comment
Overall, there are no clinically significant changes in lipid parameters in this study.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

This product generally has no withdrawal or abuse potential.

7.1.13 Human Reproduction and Pregnancy Data

This product should not be used in human reproduction or in pregnancy.

7.1.14 Assessment of Effect on Growth

This product should not be used in a Pediatric population.

7.1.15 Overdose Experience

There were no reported overdoses in this study.

7.1.16 Postmarketing Experience

There is no postmarketing experience with this product.

Adequacy of Patient Exposure and Safety Assessments

7.1.17 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Four hundred fifty-eight (458) subjects were randomized into treatment and 454 subjects received at least 1 dose of test material and were analyzed for safety. This study appears adequate to demonstrate short term safety exposure of estradiol in this product.

7.1.17.1 Study type and design/patient enumeration

Study EST-01 was a Phase 3 multi-center, randomized, placebo-controlled study to evaluate the safety and efficacy of estradiol metered dose transdermal spray in the treatment of vasomotor symptoms in postmenopausal women. Two hundred twenty six (226) subjects received the treatment drug and 228 subjects received placebo.

7.1.17.2 Demographics

Refer to Table 4 of this review; in general the majority of subjects were White 318 (70%). A total of 111(24.4%) subjects were black; the remaining subjects were Hispanic 16 (3.5%), Asian 1 (<1%), American Indian or Alaskan native 1(<1%), multi-racial 5 (1.1%) and other (2).

7.1.17.3 Extent of exposure (dose/duration)

The following table shows the extent of exposure for the 6 dosages in the trial:

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Table 16: Duration and Exposure of Total Dose in Study EST-01

	3 Sprays		2 Sprays		1 Spray	
	Estradiol (N = 76)	**Placebo (N = 75)**	**Estradiol (N = 74)**	**Placebo (N = 76)**	**Estradiol (N = 76)**	**Placebo (N = 77)**
Duration (days)*						
Mean (SD)	85.7 ± 18.2	74.1 ± 28.6	78.3 ± 21.8	79.0 ± 24.6	83.1 ± 21.5	75.9 ± 27.2
Median	85	84	85	85	86	84
Min-Max	1–126	1–112	1–113	1–105	1–125	1–116
p-value	0.0032		0.8505		0.0726	
Cumulative Exposure Time n (%) **						
≥ 84 days	62 (81.6)	48 (64.0)	55 (74.3)	55 (72.4)	61 (80.3)	48 (62.3)
70 - <84 days	9 (11.8)	10 (13.3)	7 (9.5)	10 (13.2)	8 (10.5)	13 (16.9)
56 - <70 days	0 (0.0)	4 (5.3)	4 (5.4)	1 (1.3)	0 (0.0)	4 (5.2)
40 - <56 days	2 (2.6)	0 (0.0)	1 (1.4)	1 (1.3)	0 (0.0)	1 (1.3)
28 - <40 days	0 (0.0)	4 (5.3)	3 (4.1)	3 (4.0)	4 (5.3)	5 (6.5)
14 - <28 days	2 (2.6)	4 (5.3)	1 (1.4)	1 (1.3)	1 (1.3)	1 (1.3)
< 14 days	1 (1.3)	5 (6.7)	3 (4.1)	5 (6.6)	2 (2.6)	5 (6.5)
Number of Sprays						
Mean (SD)	255.6 (55.8)	221.8 (85.5)	155.6 (44.2)	157.3 (49.3)	82.3 (22.0)	75.5 (27.3)
Median	255	252	169	170	85	84
Min-Max	3-378	3-336	2-226	2-210	1-125	1-115
p-value	0.0045		0.8278		0.0948	

7.1.18 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no secondary clinical data sources used to evaluate safety.

7.1.18.1 Other studies

There are no other studies with this product.

7.1.18.2 Postmarketing experience

There is no postmarketing experience with this product.

7.1.18.3 Literature

There is no additional literature reviews associated with this product.

7.1.19 Adequacy of Overall Clinical Experience

The sponsor presented adequate efficacy and safety data that is comparable to other estrogen products.

7.1.20 Adequacy of Special Animal and/or In Vitro Testing

There was no special animal or in-vitro testing done with this product.

7.1.21 Adequacy of Routine Clinical Testing

There were no special issues associated with the routine clinical testing in this NDA.

7.1.22 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic and clearance parameters of estradiol have been well established in the literature for over 40 years including drug-drug interactions and the effect of estradiol upon liver enzymes such as CYP450.

7.1.23 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Potential adverse events for this estradiol product have been well described in the literature and are reported in study EST-01. No new or unusual adverse events were seen in the sponsor's study. The sponsor responded early in the review process with reanalyzed primary efficacy data looking at baseline changes for each week in the treatment cycle. No further studies are recommended.

7.1.24 Assessment of Quality and Completeness of Data

The assessment of the quality and completeness of safety and efficacy is considered good.

7.1.25 Additional Submissions, Including Safety Update

The sponsor sent a submission dated June 29, 2007 stating that there have been no studies ongoing or completed and no new studies have been initiated, therefore, there are no safety data to report.

7.2 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This section is not applicable.

7.3 General Methodology

The sponsor has followed the general outline used for approval of estrogen products. Efficacy and safety data are provided are provided as a paper submission in the Common Technical Document (CTD) format with the exception of Item 11 (Case Report Tabulations) which are

submitted in electronic format (a CD0ROM is provided in Module 1 of the archival copy). This submission is organized in Modules 1 to 5.

7.3.1 Pooling Data across Studies to Estimate and Compare Incidence

There was no pooling of studies in this submission since it is supported by one Phase 3 Trial.

7.3.1.1 Pooled data vs. individual study data

There is no pooling of data vs. individual data.

7.3.1.2 Combining data

The sponsor did not combine either safety or efficacy data.

7.3.2 Explorations for Predictive Factors

Multiple Pharmacokinetic studies were conducted by Acrux Ltd. Acrux conducted early pharmacokinetic studies (FHRT001, FHRT0002,FHRT005, FHRT09, and FHRT06) using various proportions of estradiol and a penetration enhancer in order to identify an appropriate formulation and site of application that would result in therapeutic levels of estradiol when delivered via a transdermal spray. Vivus assumed and licensed development of Evamist™ from Acrux in 2004. Vivus conducted two Phase 1 clinical pharmacology studies (EST-02 and EST-06) and a Phase 3 efficacy study (EST-01).

7.3.2.1 Explorations for dose dependency for adverse findings

There were no explorations for dose dependency relating to adverse findings.

7.3.2.2 Explorations for time dependency for adverse findings

There were no explorations for time dependency for adverse findings in this study.

7.3.2.3 Explorations for drug-demographic interactions

There were no explorations for drug demographic interactions.

7.3.2.4 Explorations for drug-disease interactions

There were no explorations for drug disease interactions.

7.3.2.5 Explorations for drug-drug interactions

There are multiple drug-drug interactions that have been well documented with estrogen products. These are fully described in the class label for estrogen drug products.

7.3.3 Causality Determination

There were no unusual or unexpected causality determinations seen in the review.

8 ADDITIONAL CLINICAL ISSUES

There were no additional clinical issues to be resolved with this product.

8.1 Dosing Regimen and Administration

Submitted data suggest that the sponsor has selected the most appropriate dosing regimen for this product. Although there is delay in relief of moderate to severe vasomotor symptoms to the fifth treatment week with the 1-spray dose for severity, frequency is demonstrated in the second treatment week and continues until the 12th treatment week; efficacy is demonstrated in the 3-spray dose in the second treatment week for frequency and in the third treatment week for severity; efficacy is demonstrated in the 2-spray dose for frequency in the second treatment week and in the third treatment week for severity.

8.2 Drug-Drug Interactions

No new drug-drug interactions are identified that are not consistent with other oral or transdermal estrogen products.

8.3 Special Populations

There were no special populations studied in this submission. Estrogens are clearly not indicated fro pregnant women, nursing mothers, or pediatric use.

8.4 Pediatrics

Evamist™ is not indicated in children.

8.5 Advisory Committee Meeting

This reviewer would not recommend an Advisory Committee meeting for this product since no safety or efficacy issues were identified.

8.6 Literature Review

There was no literature review associated with this product. Previous studies with other transdermal products support safety and efficacy of estrogen when delivered by the transdermal route of administration.

8.7 Postmarketing Risk Management Plan

There are no new safety issues identified with this product.

8.8 Other Relevant Materials

The sponsor was not asked to supply any additional information except modification of efficacy data.

9 OVERALL ASSESSMENT

In study EST-01 the sponsor has supplied sufficient evidence to support the concept that the 1-spray is the lowest effective dose for Evamist™. This is demonstrated by the 1-spray dose decreasing the frequency of moderate to severe vasomotor symptoms at week 4 of treatment and severity of vasomotor symptoms (which is delayed) until week 5. Efficacy is demonstrated for the 2-spray and 3-spray dosages at week 4 and at week 12.

The 3-spray dose demonstrated efficacy that showed a small difference in efficacy between the 3-spray and 2-spray dosages (further supported by pharmacokinetic data with little difference between 2-spray and 3-spray in regards to C_{max} and C_{aver}). The sponsor supplied additional data that showed the 3-spray dose provides an increased systemic estradiol concentration when compared to the 2-spray dose. Estrone levels were also higher on days 3 to 13 in study EST-02. Overall, the estradiol/estrone levels demonstrated by Evamist™ in clinical study EST-01 at the 3-spray dose are lower than many approved estrogen transdermal products and do not appear to represent any additional safety risk to subjects.

9.1 Conclusions

This reviewer concludes that the lowest effective dosage of Evamist™ is the 1-spray dose. The 1-spray, 2-spray and 3-spray dosages provide acceptable efficacy and safety and should be approved. It is recommended that a subject start with the 1-spray dose and titrate upward to achieve sufficient relief of symptoms.

9.2 Recommendation on Regulatory Action

A letter of approval should be sent to the sponsor.

9.3 Recommendation on Postmarketing Actions

There are no recommendations regarding post marketing action.

9.3.1 Risk Management Activity

There is no additional risk management activity for the sponsor.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

See section 9.7

9.5 Comments to Applicant

There are no direct comments from this reviewer to the applicant.

9.6 Review of Individual Study Reports

9.7 Line-by-Line Labeling Review

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Phill H. Price
7/27/2007 10:45:28 AM
MEDICAL OFFICER

Shelley Slaughter
7/27/2007 11:58:22 AM
MEDICAL OFFICER
I concur with Dr. Price's conclusions on efficacy and safety of Evamist and his recommendation for approval. See also my Team Leader Review.