CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-014	Submission Date(s): 09/28/2006, 03/28/2007, 04/06/2007, 05/04/07, 06/15/2007
Brand Name	EvaMist®
Generic Name	Estradiol Transdermal Spray
Reviewer	PeiFan Bai, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Vivus, Inc
Relevant IND(s)	— b(4)
Submission Type; Code	Original
Formulation; Strength(s)	Topical spray, 1.7% w/v, 90µl/spray
Indication	Treatment of moderate-to-severe vasomotor symptoms associated with menopause

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1 Executive Summary

1.1 Recommendation

DCP-III/OCP finds NDA 22-014 acceptable from a clinical pharmacology perspective provided the labeling comments are adequately addressed.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

EvaMist® is an estrogen indicated for treating moderate to severe vasomotor symptoms (VMS) associated with menopausal women. EvaMist® is formulated as a solution of estradiol and octisalate in ethanol delivered as a transdermal spray (metered dose transdermal spray, MTDS). The metered dose pump delivers 90 µl (1.53 mg of estradiol) per spray in vitro, and 21µg/1 spray, 37 µg/2 sprays, and 36 µg/3 sprays in vivo. The in-vivo delivery rate was estimated based on Cavg and CL from the population kinetics. The estradiol contained in EvaMist® is chemically identical to the naturally occurring human estradiol. The proposed doses are 1 spray, 2 sprays, and 3 sprays. When applying more than 1 spray, the additional sprays are to be applied beginning near the elbow to separate, adjacent, non-overlapping areas on the same forearm. The application site(s) should be allowed to dry for 2 minutes before covering the area with clothing and to refrain from washing the site for 30 min after each application. The to-be-marketed formulation was studied in several PK studies (EST-06: transferability study, washing effect, and effect of sunscreen; EST-02: steady state pharmacokinetics; FHRT-06: effect of application sites) and phase III trial (EST-01).

Steady state pharmacokinetics: Study EST-02 was a parallel study involving 72 subjects with 24 female subjects in each treatment group. Three treatment groups were 1 spray, 2-spray, and 3-spray groups. Serum concentrations of estradiol, estrone, and estrone sulfate were determined on Day 14. There was no dose proportionality for estradiol, estrone or estrone sulfate when dose increased from 1 spray to 3 sprays based on the data from Day 14. For estradiol, AUCs were similar between 2 sprays and 3 sprays, so were Cmax values. For estrone and estrone sulfate, the increases in AUC and Cmax from 1 spray to 2 sprays, though not dose proportional, were much higher than those from 2 sprays to 3 sprays. The Tmax of estradiol from the three doses studied ranging from 10 hrs to 20 hrs. There was substantial fluctuation in serum concentration profiles at steady state. In its amendment of June 15, 2007, the firm pointed to the Day 1-Day 13 predose levels showing a trend of increase with dose; that is the 3-spray dose had higher exposure than the 2-spray dose and the 2-spray dose higher than the 1-spray dose.

Transferability study, washing effect, and effect of sunscreen: Study EST-06 consisted of three studies using the same group of subjects (n=20) and lasted for 18 days. The dose administered was three 90 µl sprays daily. The three studies were skin-to-skin transfer, effect of washing 1 hr after application, and effect of sunscreen. The contact between the female's subject treated inner forearm was held tightly (without rubbing or movement) against the inner forearm of a male subject for 5 minutes (continuous contact). No significant amount was transferred between the female subject and her partner. Washing 1 hr after application with warm soapy water only slightly increased AUC(0-24) and shortened tmax by 1 hr. Sunscreen applied 1 hr prior to or after spray application did not change the exposure substantially. Sunscreen applied 1 hr post dose lowered estradiol AUC by 11% as compared to no sunscreen.

Inner thigh as the alternate site: Study FHRT-06 (n=11) was a crossover study comparing two application sites, inner forearm and inner thigh. Two 90 µl sprays were applied once daily to adjacent sites on the ventral forearm or inner thigh for 7 days. Application to the inner thigh produced higher mean serum estradiol and estrone levels than application to the forearm. Based on the baseline-corrected pharmacokinetics of the 2-spray dose, application to the inner thigh was not bioequivalent to application to the forearm with 90% CI of 83.2%-149% for AUC0-24 and 86.6%-189% for Cmax. After the June-5-2007 teleconference with the firm regarding the non-bioequivalence issue, b(4)

Clinical trial: Study EST-01 was conducted at 43 sites and involved 444 subjects with 428 subjects included in the efficacy evaluable analysis. Three doses (1-spray, 2-spray, 3-spray) were studied with estradiol applied to the inner form. The study was 13 weeks long. Samples for estradiol, estrone, and estrone sulfate were collected during routine study visits. The unadjusted post-dose serum estradiol levels at week 4, week 8, and week 12 showed a trend of increase with

dose, though not dose-proportional. Two clinical endpoints evaluated were reduction in hot flush frequency and severity score. The 2-spray dose was statistically significantly different from placebo at weeks 4 and 12 in the treatment of moderate to severe VMS. A positive treatment effect was observed at week 2-3 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 for the 1-spray dose and this continued through week 12. There was no dose response relationship based on the data on Day 14. For sex hormone binding globulin (SHBG), the percent increase from baseline was higher in the 3-spray estradiol group (16.9%) as compared to the 3-spray placebo group (5.7%). The changes in SHBG levels are within the range of past-approved products. Based on the firm's June 15, 2007 amendment, the estradiol exposure (taken from prior to treatment during visits at weeks 4, 8, and 12) were higher in those responders showing 75% reduction at weeks 4 and 12. The reductions in the severity scores were significantly higher in the 3-spray group than in the 2-spray and 1-spray groups.

2 Question Based Review

2.1 General Attributes

2.1.1 What is EvaMist?

EvaMist is a metered dose transdermal spray (MTDS) of estradiol for treating VMS in postmenopausal women. EvaMist contains a homogeneous solution of 1.7% estradiol (USP) and — octisalate (USP) in alcohol (USP) formulated to provide a sustained delivery of the active ingredient into the systemic circulation. EvaMist is designed to deliver estradiol to the blood circulation following topical application to the skin of a rapidly drying solution from MDTS. The metered dose pump delivers 90 µl (1.53 mg of estradiol) per spray in vitro and 25 µg per spray in vivo. The average drying time of 1 spray was 90 sec (median 67 sec).

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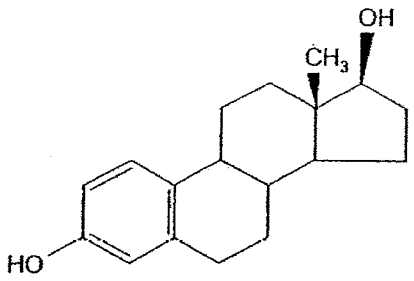
The structural formula of estradiol is:



2.1.2 What is the proposed indication of EvaMist?

EvaMist is to treat moderate-to-severe VMS associated with menopause.

2.1.3 What are vasomotor symptoms (VMS)?

Before the menopause, the primary source of estrogen is ovarian 17ß-estradiol and its production is regulated by gonadotrophin follicle-stimulating hormone (FSH). Estradiol is metabolized to less potent metabolites, estrone (12 times less) and estriol (80 times less). Estrone may be converted back to estradiol. Estriol is the major urinary metabolite. A variety of sulfate and glucuronide conjugates also are excreted in the urine (In: Goodman and Gilman's, 9th edition; Drugs 40(4) 561-582, 1990).

In pre-menopausal women, during the early follicular stages the serum concentrations of both estradiol and its metabolite, estrone, are typically between 40 and 60 pg/m, with estradiol concentration increasing to 200 to 400 pg/mL and estrone level to 170 to 200 pg/mL during the late follicular phase. In postmenopausal women, the major source of estrogen is androstenedione, which is metabolized to estrone, which may be subsequently converted to estradiol. Therefore, in postmenopausal women, serum estradiol level is reduced to about 5 to 20 pg/mL and estrone concentrations between 30 and 70 pg/mL with the ratio of estradiol to estrone being 0.2 to 0.3, compared with >1 in premenopausal (Drugs 40(4) 561-582, 1990).

In postmenopausal women, ovarian activity is lost and menstruation stops. One of the typical symptoms that postmenopausal women experience is 'hot flush,' the so-called VMS. Hot flush occurs in 75 – 85% of postmenopausal women for an average duration of 1 – 2 years. The cause of VMS is unknown but believed to occur due to induced liability in the thermoregulatory center of the hypothalamus with declining levels of estrogen and progesterone resulting in peripheral vasodilation. Hot flush symptoms include sudden onset of reddening of the skin over the head, neck, and chest, feeling of intense body heat with duration of a few seconds to minutes, and rarely for up to an hour, and sometimes profuse perspiration. Each episode coincides with a surge in luteinising hormone (LH). The severity is defined as follow:

Mild:	sensation of heat without sweating
Moderate:	sensation of heat with sweating, able to continue activity
Severe:	sensation of heat with sweating, unable to continue activity

2.1.4 What is the proposed mechanism of action of EvaMist?

Hormonal supplement of estrogen has been used to alleviate VMS associated with menopause by increasing the serum estradiol levels in postmenopausal women. EvaMist delivers estrogen systemically via the transdermal route, which bypasses hepatic first-pass metabolism. By increasing the serum estradiol levels in postmenopausal women, EvaMist alleviates moderate-to-severe VMS.

2.1.5 What are the proposed dosage and route of administration?

EvaMist is to be applied topically to the inner surface of the forearm starting near the elbow. EvaMist therapy is to be initiated with one spray per day with each spray delivering 90µl (1.53 mg of estradiol) in vitro. One spray of EvaMist delivers approximately 0.021 mg/day of estradiol to the systemic circulation. Dose adjustments should be guided by the clinical response. One spray, two sprays, and three sprays deliver 1.53 mg, 3.06 mg, or 4.59mg of estradiol to the skin, respectively. One, two or three sprays are applied daily to adjacent non-overlapping (side-by-side) 20 cm^2 areas on the inner surface of the arm between the elbow and wrist and allowed to dry.

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2.1.6 What are current approved treatments for VMS?

There are many estrogen alone and estrogen plus progestin drug products currently approved for the treatment of moderate to severe VMS associated with the menopause. Please refer to Medical Officer's review for a complete list.

2.1.7 What is the process of formulation development?

The FHRT-0001 study compared the pharmacokinetic parameters of a MDTS (same device as used in EvaMist) containing ' with those of Estraderm 50 Patches (NDA 019081, approved September 10, 1996, manufactured by Novartis Pharma Ag., Switzerland. The patch contains 4 mg of 17-ß-estradiol and with a nominal in vivo release rate of 50µg/24 hrs from an area of 10 cm2. Application site: abdomen). Estraderm 50 showed slightly higher AUC than MDTS. From this study, the firm decided to fix the ratio of estradiol to octisalate to be — Several exploratory studies used a formulation slightly different from the final formulation. These studies (FHRT-0001, FHRT-0002, FHRT-0005, and FHRT-09) used the same solvent (ethanol) and absorption enhancer (octisalate) but with estradiol and octisalate at lower concentrations and lower spray volumes. The details of the formulations used for these individual studies are as follows: FHRT-0001 , FHRT-0002 , FHRT-0005 and FHRT-09

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The proposed commercial formulation of EvaMist is the same as that used for the several PK studies, including EST-01 (phase 3 safety and efficacy trial), EST-02 (steady state PK profile in healthy postmenopausal women), EST-06 (the effects of skin-to-skin contact, application site washing and sunscreen use), and FHRT-06 (a PK study to assess the effect of different application sites).

Table 1: List of pharmacokinetic characterization studies of the final formulation

Study #	Dose (g/day) (in-vitro dose unless noted otherwise)	Duration	Site of Application	PK measurements
EST-02	A (90µl), B (2X 90µl), or C (3X 90µl)* Estimated in vivo doses are 25 µg, 50 µg and 100 µg	14 days	Inner forearm	AUC, Cmax, Tmax, Cmin, and Tmin
EST-06	90µl X 2 (50 µg)	17 days**	Inner forearm	AUC, Cmax, Tmax,
FHRT-06	90µl X 2 (estimated in-vivo dose: 50 µg)	7 days	Ventral forearm and inner thigh	AUC, Cmax, Tmax, Cmin, and Tmin, Cavg

Note: *The proposed dose are one spray (90µl), two sprays (2X 90µl), and three sprays(3X 90µl), releasing 1.53mg, 3.06mg, or 4.59 mg of estradiol in-vitro to the skin, respectively.
**: In 17 days, studies of washing, transferability, and effect of sunscreen were conducted.

Table 2: The proposed commercial formulation

Ingredient	Strength % w/w	Strength % w/v	Content/vial	Function	Compendial Monograph
Estradiol	—	1.7	—	Active Ingredient	USP
Octisalate	—	—	—	Penetration Enhancer	USP
Alcohol	—	—	—	Solvent	USP

*Includes 1% overage for evaporation losses

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2.2 General Clinical Pharmacology

2.2.1 What are the pharmacokinetic (PK) characteristics of the drug and its major metabolites?

According to the Physicians' Desk Reference, estrogen is well absorbed through the skin, mucous membranes, and the gastrointestinal tract. Exogenously-delivered or endogenously-derived estrogens are primarily metabolized in the liver to estrone and estriol, which are also found in the systemic circulation. Estrogen metabolites are primarily excreted in the urine as glucuronides and sulfates.

The steady state pharmacokinetic parameters were determined in Study EST-02 (a parallel study involving 72 healthy postmenopausal women with 24 subjects in each treatment group). Baseline median concentrations (Day 0 at 8:00 pm) were 3, 3.45, and 3.8 pg/ml, respectively, for the 1-spray, 2-spray, and 3-spray groups. The pharmacokinetic parameters of estradiol, estrone, and estrone sulfate on day 14 after 14 days of inner-forearm administration of one, two, and three 90µl sprays are discussed below.

Estradiol: The pharmacokinetic parameters are summarized in the table below. The firm did not determine the half-life of estradiol administered from EvaMist.

Table 3. Mean* (CV%) unadjusted estradiol pharmacokinetic parameters (Day 14)

	1-spray group (n=24)	2-spray group (n=23)	3-spray group (n=24)
AUC0-24 (pg*hr.ml)	471 (49)	736(43)	742(30)
Cmax (pg/ml)	36.4 (62)	57.4(94)	54.1 (50)
Cmin (pg/ml)	11.3 (52)	18.1 (51)	19.6(27)
Cavg(pg/ml)	19.6 (49)	30.7(43)	30.9(30)
Tmax[b]	20(0-24)	18 (0-24)	20 (0-24)
DF%	126(65)	115(86)	105(60)

* Arithmetic mean unless noted otherwise; b: median (Minimum-maximum);
DF%= [(Cmax-Cmin)/Cavg]*100%

AUC, Cmax, Cmin, and Cavg were similar between 2-spray and 3-spray doses. From the daily dose range of 1 spray to 3 sprays, there was no dose proportionality for the steady state AUC, Cmax, Cmin or Cavg according to the unadjusted serum pharmacokinetic parameters of estradiol on Day 14. However, the pre-dose levels from Day 1 to Day 13 showed a trend of increase with

dose. The median Tmax remained similar for all three doses, around 18-20 hours. The Day 21 (8:00 am) median concentrations were 4.73 pg/ml (1 spray), 5.38 pg/ml (2 sprays), and 6.47 pg/ml (3 sprays).

Estrone: The unadjusted pharmacokinetic parameters of estrone, a major metabolite of estradiol, seemed to show a slight trend of increase in AUC, Cmax, Cmin, and Cavg with increased daily dose.

Table 4. Mean* (CV%) unadjusted estrone pharmacokinetic parameters (Day 14)

	1-spray group (n=24)	2-spray group (n=23)	3-spray group (n=24)
AUC0-24 (pg*hr.ml)	886 (29)	1208 (26)	1367(30)
Cmax (pg/ml)	49.6 (34)	60.2 (25)	71.4 (37)
Cmin (pg/ml)	30.3 (31)	41 (29)	46.5 (32)
Cavg(pg/ml)	36.9 (29)	50.3 (26)	57(30)
Tmax[b]	17 (0-24)	10 (0-24)	10 (0-24)
DF%	54 (73)	39 (44)	43 (66)

* Arithmetic mean unless noted otherwise; b: median (Minimum-maximum);
DF%= [(Cmax-Cmin)/Cavg]*100%

Estrone sulfate: The unadjusted pharmacokinetic parameters of estrone sulfate showed a slight trend of increase in AUC, Cmax, Cmin, and Cavg with increased daily dose.

Table 5. Mean* (CV%) unadjusted estrone sulfate pharmacokinetic parameters (Day 14)

	1-spray group (n=24)	2-spray group (n=23)	3-spray group (n=24)
AUC0-24 (pg*hr.ml)	16502 (58)	26515(45)	27971 (45)
Cmax (pg/ml)	1099.8 (76)	1543 (47)	1656.6 (43)
Cmin (pg/ml)	485.7 (58)	700.7 (54)	781.3 (47)
Cavg(pg/ml)	687.6 (58)	1104.8(45)	1165.5(45)
Tmax[b]	9 (0-24)	8 (0-24)	10 (0-24)
DF%	86 (70)	74 (41)	77 (34)

* Arithmetic mean unless noted otherwise; b: median (Minimum-maximum);
DF%= [(Cmax-Cmin)/Cavg]*100%

Effect of EvaMist administration on Sex Hormone binding globulin (SHBG) concentrations.

SHBG changes due to topical application of estradiol were determined in Phase III trial (EST-01) in the 3-spray group at visit 2 (baseline) and visit 5 (week 12). Relative to the baseline level, the percentage change in SHBG was approximately 14.5% at week 12 for the estradiol 3-spray group and 5.2% in the placebo-3 sprays group.

Table 6: Summary of SHBG results

	Estradiol 3-spray	Placebo 3-spray
	Week 12	Week 12

N	38	39
Mean (SD) (nmol/L)	53.8 (24.95)	66.8 (34.14)
Median	48.9	64
Baseline	46.2	63.2
% change from baseline	16.9%	5.7%

Table 7. Change from baseline in SHBG levels in subjects in the 3-spray dose group, ITT/safety population.

	Estradiol 3-spray	Placebo 3-spray
N	38	39
Mean (SD) (nmol/L)	7.8 (11.53)	3.3 (14.57)
p-value**	0.0002	0.1802
p-value***	0.1433	

*n=number of subjects with paired data
** Test for significant change from baseline within group using a paired t-test
*** test for treatment difference in change from baseline using t-test.

Comments: The percent increase of SHBG in the estradiol-treated group is not much different from what were observed in other NDAs, such as 21-813 (Elestrin®), which showed a less than 15% increase.

2.2.2 What is the estradiol exposure following EvaMist application relative to that of other approved estradiol topical products?

The following table summarizes the PK parameters in the labels of other approved estradiol products (rounded to the nearest integer) along with those of EvaMist for comparison. Compared to other approved products, EvaMist has the lowest dose. From the one spray dose of 0.00153g, EvaMist has higher Cave than Elestrin (gel) (0.87 g). From the two-spray dose of 0.003g or the three-spray dose of 0.046g, EvaMist has an estradiol exposure higher than Climara (0.025g) and Elestrin (gel)(0.87 g).

Table 7: PK parameters for EvaMist and other topical estradiol products listed in the PDR.

Drug	Strength (mg/day or as indicated)	AUC (pg.h/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	C_{ave} (pg/mL)
Climara	0.025		32	17	22
Climara	0.05		71	29	41
Climara	0.1		147	60	87
Climara (applied to buttock)	0.1		174	71	106
Vivelle	0.025		46	30	34
Vivelle	0.0375		83	41	57
Vivelle	0.075		99	60	72
Vivelle	0.1		133	90	89
Vivelle (applied to buttock)	0.1		145	85	104
Estrasorb	0.05			70.2	
Estrogel	1250		46.4		28.3
Elestrin	870	335	22	9	15
Elestrin	1700	940	67	21	39

EvaMist*	1.53 (1 spray)	471	36.4	11.3	19.6
EvaMist*	3.6 (2 sprays)	736	57.4	18.1	30.7
EvaMist*	4.6 (3 sprays)	742	54.1	19.6	30.9

Note: This table was adapted from NDA 21813 QBR CP review.doc with information for EvaMist added.

2.2.3 What are the characteristics of ADME?

There is no report on the half-life of estradiol from the sponsor. From the literature, the true half-life of estradiol is approximately 15 hrs. Tmax was 18-20 hrs after 1 spray, 2 sprays, and 3 sprays. Cmax was 36.4 pg/ml after 1 spray, 57.4 pg/ml after 2 sprays and 54.1 pg/ml after 3 sprays.

The distribution, metabolism and excretion of estradiol are well known and have been summarized in the Guidance for Industry: Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommended Prescribing Information for Health Care Providers and Patient Labeling. The following paragraphs are from the guidance.

> The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.
>
> Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic inter-conversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.
>
> Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

2.2.4 What is the linearity or nonlinearity of dose-concentration relationship?

Considering the relationship between dosing rate and average concentration at steady state,

$F*Dose/\tau = Cave.ss * CL$

Where F is bioavailability, $Dose/\tau$ is dosing rate, Cave.ss is average concentration at steady state, and CL, clearance.

Though the levels of endogenous estradiol and metabolites may fluctuate, the baseline-corrected data are more appropriate for assessing whether the dose-concentration relationship is linear. There are two studies that reflect steady state, study EST-01 and study EST-02. Though Study EST-01 had only one sample measured (2-6 hr post dose) for visits at weeks 4, 8, and 12, it has a larger number of subjects. The results are worth of discussion. Study EST-02 had a complete concentration/time profile at steady state after dosing for multiple days.

Study EST-02. The firm used the baseline-adjusted results from EST-02 for such analysis. The baseline-unadjusted data from Study EST-02 are summarized in Table 8.

Table 8. Some mean* (CV%) baseline-adjusted estradiol pharmacokinetic parameters (Day 14)

		1-spray group (n=24)	2-spray group (n=23)	3-spray group (n=24)
AUC0-24 (pg*hr.ml)	Arithmetic mean	375 (60)	654 (49)	646 (43)
	Geometric mean	325 (58)	584 (52)	623 (46)
Cmax (pg/ml)	Arithmetic mean	32.4 (70)	54 (100)	49.8 (59)
	Geometric mean	26.4 (73)	42.1(73)	45.1 (61)
Cavg(pg/ml)	Arithmetic mean	15.6 (60)	27.3 (49)	26.9 (43)
	Geometric mean	13.5 (58)	24.3 (52)	25.9 (46)

Since the pharmacokinetic parameters have a log normal distribution, it is reasonable to use log-transformed data for statistical determination of the linearity or non-linearity dose-concentration relationship. The firm used the regression of ln(parameter)=a+ b* ln(Dose)+error where "a" is the intercept and "b" is the slope to determine dose-parameter relationship. The 'b" for lnAUC was 0.62, and 'b" for lnCmax 0.51, far less than 1.

Based on the Day-14 data, the baseline-adjusted steady state geometric mean of AUC (0-24) increased as the dose increased from 1 spray to 2 sprays but then did not change much as the dose increased from 2 sprays to 3 sprays, as shown in Figure 1 below.

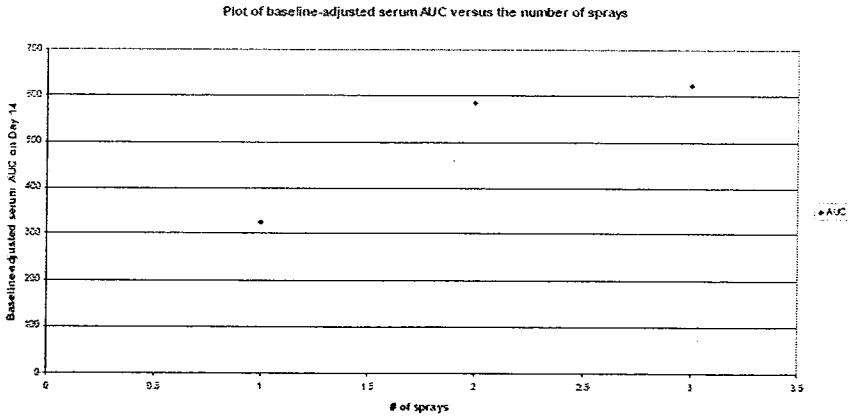
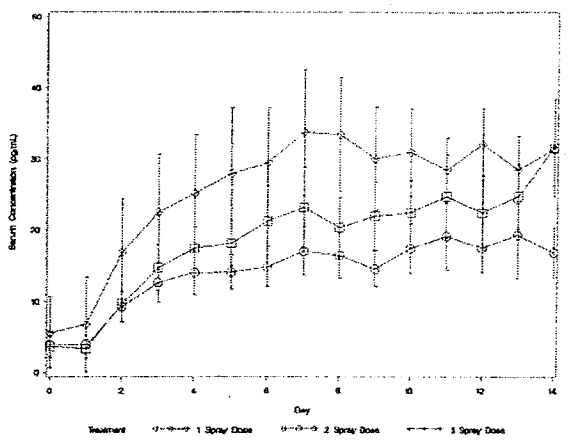


Figure 1.

The following figure is copied from the June 15, 2007 amendment.

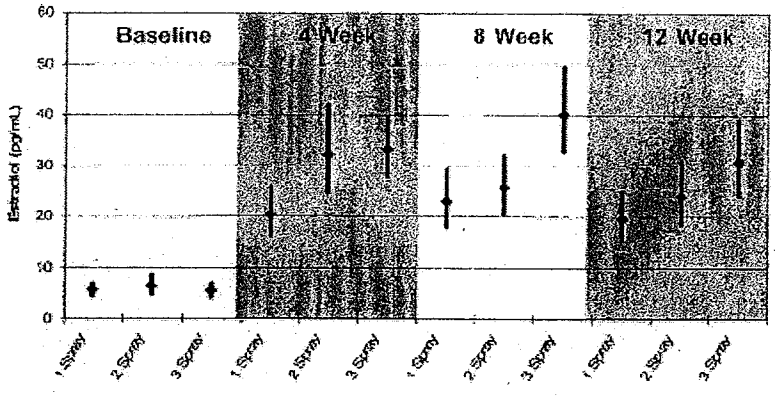
Figure 2. Mean (SE) unadjusted pre-dose estradiol concentrations (Day 0-14)



Comment on the results of study EST-02: Based on the Day 14 data, there is no dose proportional increase in the steady state pharmacokinetic parameters. However, the pre-dose estradiol levels did increase with dose, though not proportionally, based on the pre-dose levels from Day 1 to Day 13.

EST-01: Since EST-01 had more than 400 participants with more than 45 subjects in each spray group of estradiol and placebo treatments, the results are discussed here as well. Mean (95% CI) baseline estradiol levels were uniform (5.1 (4.0, 6.5)-6.4 (4.8-8.6) pg/mL) across all treatment groups and remained at low levels (3.9 (3.5, 4.5)-6.0 (4.5-8.1) pg/mL) throughout the study in placebo subjects. Below figure 3 showed a comparison of the geometrical mean of unadjusted estradiol concentration between baseline and weeks 4, 8, and 12. It is clear from the figure that there is no linear dose-concentration relationship.

Figure 3. Mean (95%) unadjusted serum estradiol levels following treatment with estradiol transdermal spray.



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

2.2.5 Does application site have an effect on drug absorption?

Study FHRT-06 (n=11) was a crossover study comparing two application sites, inner forearm and inner thigh. Two 90 µl sprays were applied once daily to adjacent sites on the ventral forearm or inner thigh for 7 days. Application to the inner thigh produced higher mean serum estradiol and estrone levels than application to the forearm. Based on the baseline-corrected pharmacokinetics of the 2-spray dose (table 9), application to the inner thigh was not bioequivalent to application to the forearm with 90% CI of 83.2%-149% for AUC0-24 and 86.6%-189% for Cmax.

Table 9. Summary of baseline-corrected estradiol pharmacokinetic parameters.

Parameter	(Estradiol MDTS 1.7% forearm) Mean ± SD	(Estradiol MDTS 1.7% inner thigh) Mean ± SD
AUC (pg* hr /ml)	730 ± 428	852 ± 565
Cmax (pg/ml)	52 ± 28.4	82.2 ± 74.9
Cmin (pg/ml)	15.4 ± 9.1	13.1 ± 7.3
Cavg (pg/ml)	30.4 ± 17.8	35.5 ± 23.5
DF (%)	124 ± 31	159 ± 72
Ratio AUC0-24 Estradiol/Estrone	1.17 ± 0.38	1.15 ± 0.73

Amendment 11 submitted June 15, 2007: The Agency held a teleconference with the firm. One of the issues discussed in the teleconference was the exposures from inner thigh and inner arm were not bioequivalent. After being presented with the Agency's comments, b(4)

2.2.6 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The to-be-marketed formulation was studied in several PK studies (EST-06: transferability study, washing effect, and effect of sunscreen; EST-02: steady state pharmacokinetics; FHRT-06: effect of application sites) and phase III trial (EST-01).

Steady state pharmacokinetics: Study ES-02 was a single-center, randomized, open-label, parallel group study, 72 healthy naturally or surgically postmenopausal women, aged 40 to 65 years, were randomly assigned to receive one of three dose levels (24 subjects per treatment) of estradiol metered-dose transdermal spray (MDTS) applied to the inner forearm of the same arm once daily for 14 days. From the study, the firm determined the predose levels (trough serum concentration) of estradiol. Three treatment groups were 1 spray group, 2-spray group, and 3-spray group. Serum concentrations of estradiol, estrone, and estrone sulfate were determined on Day 14 for complete concentration/time profiles and calculations of steady state pharmacokinetic parameters.

Transferability study, washing effect, and effect of sunscreen: Study EST-06 was a single-center, open-label study, three 90 µl sprays of estradiol MTDS were applied daily to the inner forearm of 20 females for 18 days. Study EST-06 consisted of three studies using the same group of subjects (n=20) and lasted for 18 days. For the transferability, 20 healthy male subjects participated on Days 1-3. The washing effect was done Day 10 (control) and Day 11(Washing). For the effect of sunscreen, 20 subjects were randomly divided into two groups with Group 1 had sunscreen applied 1 hr prior to estradiol application on Day 14 and 1 hr after estradiol application Day 17. The dose administered was three 90 µl sprays daily. The three studies were skin-to-skin transfer, effect of washing 1 hr after application, and effect of sunscreen.

Inner thigh as the alternate site: Study FHRT 06 was a single centre, open label pharmacokinetic study in healthy postmenopausal women using a randomized, three-way, cross-over design. Study FHRT-06 (n=11) was a crossover study comparing two application sites, inner forearm and inner thigh. Two 90 µl sprays were applied once daily to adjacent sites on the ventral forearm or inner thigh for 7 days. Application to the inner thigh produced higher mean serum estradiol and estrone levels than application to the forearm. Statistical bioequivalence analysis was performed using the baseline-corrected data.

Clinical trial: Study EST-01 was conducted at 43 sites and involved 444 subjects with 428 subjects included in the efficacy evaluable analysis. The patients were instructed and given dietary cards for daily recording of frequency and severity of hot flashes. The efficacy of the three doses studied was determined based on the changes from the baseline. The firm also measured the post dose levels of estradiol and its metabolites at weeks 4 and 12. Three doses (1-spray, 2-spray, 3-spray) were studied with estradiol applied to the inner form. The study was 13 weeks long. Samples for estradiol, estrone, and estrone sulfate were collected during routine study visits. SHBG levels were also determined at baseline and at week 12 visit.

2.2.7 Are the active moieties in the plasma (or other biological fluids) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Serum concentrations of estradiol and its metabolites, estrone and estrone sulfate and their pharmacokinetic parameters were appropriately measured for the estimation of their pharmacokinetic parameters. Serum concentrations of estradiol and its metabolites, estrone and estrone sulfate, were identified and measured along with the records of frequency and severity score of VMS from patients' diaries for exposure/response relationship. Furthermore, plasma levels of sex hormone binding globulin were also measured.

2.2.8 What are the characteristics of the dose-response relationship for efficacy?

Currently the FDA recommends 2 primary endpoints for demonstrating the efficacy of treating VMS. They are 1) statistically significant mean change in frequency from baseline to week 4 and week 12 (clinically significant reduction in hot flush frequency of at least two hot flushes above placebo at week 4 and week 12), and statistically significant mean change in severity from baseline to week 4 and week 12.

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

The information from the following 2 tables is from Dr. Phil Price's review.

Table 10. Reduction in the number of moderate to severe hot flushes of three doses

	3 sprays		2 sprays		1 spray	
	estradiol	placebo	estradiol	placebo	estradiol	placebo
N	76	75	76	75	76	77
Week 4	-6.64	-4.54	-7.30	-4.74	-6.26	-3.64
Week 12	-8.44	-5.32	-8.66	-6.19	-8.10	-4.76

Table 11. Reduction in severity score of moderate to severe hot flushes of three doses

	3 sprays		2 sprays		1 spray	
	estradiol	placebo	estradiol	placebo	estradiol	placebo
N	76	75	76	75	76	77
Week 4	-0.43*	-0.13	-0.57**	-0.25	-0.47***	-0.17
Week 12	-1.07*	-0.31	-0.92**	-0.54	-1.04***	-0.26

*p<0.003 at week 4 and p<0.001 at week 12

** P < 0.0160 at week 4; p < 0.0406 at week 12

***At week 4 the p value is 0.0573; at week 12 p = <0.0001

The following comments are taken from Dr. Phil Price's review before the Agency received the June 15, 2007 amendment:

A statistically significant ($p < 0.01$) reduction was observed in the frequency of moderate to sever 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 2-spray dose was statistically significantly different from placebo at weeks 4 and 12 in the treatment of moderate to severe vasomotor. A positive treatment effect was observed at week 2-3 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 for the 1-spray dose and this continued through week 12. There was no dose response relationship.

Overall, it appears that depending on the number of subjects in the treatment groups, the 3 dosages performed as expected (e.g. greater difficulty in achieving statistical significance in the age group < 50) in the treatment of vasomotor symptoms for a transdermal product that is applied on a daily basis. Because the study was not powered to assess primary endpoint differences in any subgroup population, the results for the subgroups analyzed do not show reproducibly statistically significant differences between treatment and placebo. In subjects who were < 50 years of age, were surgically menopausal, and had a BMI <=25kg/m^2 the 3-spray, 2spray, and 1-spray groups were less effective at week 4 but demonstrated greater efficacy at week 12. This is relevant because the subject's age, surgical status at menopause and BMI are known parameters that impact upon the overall efficacy of subjects who are receiving hormonal therapy.

Reviewer's comments on the Amendment 11 (June 15, 2007): The firm submitted additional exposure/response data to support its claim that the 3-spray dose should be made available in its letter of June 15, 2007. The firm submitted Supplement Table 1 and indicated that the mean pre-dose serum estradiol concentrations were the highest in the 3-spray group, followed by the 2-spray group, and then by 1-spray group based on the measurements taken at weeks 4, 8, and 12 (ES-01). There is a slight exposure/response relationship in terms of reduction in the number of moderate to severe of hot flushes or in the severity score. For the responders who showed 75% reduction in the frequency of hot flushes had higher estradiol exposure than the non-responder. The reductions in the severity scores were significantly higher in the 3-spray group than in the 2-spray group. The 3-spray dose is effective.

2.2.9 What are the characteristics of the dose-response relationship for safety?

The following table is adopted from Dr. Phil Price's review.

Table 12. Overall Adverse Events

	3Sprays		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.

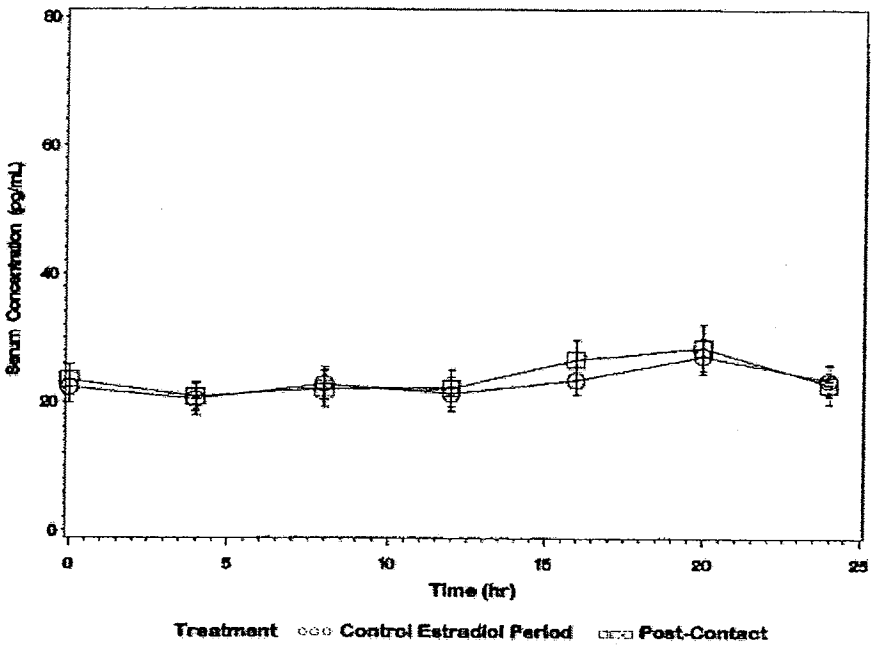
Dr. Price's Comments: Note than 12 subjects withdrew from the study, 6 in the estradiol treatment group and 6 in the placebo groups. In the estradiol groups, 5 subjects were withdrawn due to adverse events considered related to treatment (ovarian cyst, headache, nipple pain, chest pain and nausea). Three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

Comments: Based on the data from Dr. Phil Price's review, there is no dose-response relationship for safety.

2.2.10 What is the exposure to estradiol following direct contact with a partner?

Less than 4% increase in estradiol AUC in the experimental group as compared with the control group. Minimal or negligible exposure to estradiol was observed following direct forearm to forearm contact with a partner.

Figure 4. Skin-to-skin transfer study: Mean (SEM) unadjusted estradiol serum concentrations (male subjects)



2.2.11 What is the effect of washing on the pharmacokinetic parameters of estradiol?

Table 13a. Washing effect study: Mean (CV%) of unadjusted estradiol pharmacokinetic parameters (female subjects)

PK Parameter	N	Control Estradiol	N	Washing
$AUC_{(0-24)}$ (pg•hr/mL)[a]	20	869.15 (71.08%) 734.72 (60.60%)	20	939.79 (82.36%) 756.85 (69.30%)
C_{max} (pg/mL)[a]	20	62.68 (82.15%) 48.91 (79.69%)	20	61.01 (98.25%) 45.88 (80.64%)
T_{max} (hr)[b]	20	18.00 (0.00-24.00)	20	17.00 (0.00-22.00)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)

[b] Median (minimum-maximum)

Table 13b. Washing effect study: Statistical analysis of log-transformed AUC(0-24) for Baseline-corrected estradiol serum concentrations (female subjects).

PK Parameter	Washing (B) N = 19	Control Estradiol (A) N = 19	Ratio B/A	90% CI
ln $AUC_{(0-24)}$	625.25	600.69	1.04	0.92-1.18

Washing seemed to increase the AUC and Cmax of estradol slightly. The washing procedure of using warm water might have actually facilitated the circulation beneath skin, thereby facilitating the transport and absorption of estradiol from the skin to the systemic circulation.

2.2.12 Is the calculation of in vivo delivery rate acceptable?

Delivery rate desired = Cave, ss (average concentration at steady state) (pg/ml) * clearance rate.

Where estradiol clearance rates were estimated to be approximately 13.1 ml/kg/min or 1350 L/day or 1280 L/day in a 70 kg woman (according to NDA 21813 review). Based on the baseline-adjusted average concentrations of estradiol observed in EST-02 study for 1 spray, 2 sprays, 3 sprays, the in-vivo delivery rates ranged from 19.97-21.06 μg, 34.94-36.86 μg, and 34.4-36.32 μg, respectively. The average of the Day 0 (8:00 pm) and Day 1(8:00 am) were used for baseline correction. In the clinical report (Module 2, Vol 1, page 71 of 183), the firm stated that systemic delivery of estradiol ranged from approximately 20 μg/day for the 1-spray dose, to approximately 40 μg/day for the 3-spray dose. The calculated in-vivo delivery rate is 0.021 mg/1day based on the baseline-adjusted Cavg of 15.6 pg/ml for 1 spray. The calculated in-vivo delivery rate from 2 sprays is 0.037 mg/day based on the baseline-adjusted Cavg of 27.3 pg/ml. The calculated in-vivo delivery rate from 3 sprays is 0.036 mg/day based on the baseline-adjusted Cavg of 26.9 pg/ml.

Using the above equation, a daily delivery of 50 μg of estradiol to the systemic circulation would be expected to produce an average baseline adjusted serum estradiol levels of approximately 37 pg/ml. In Phase 1 studies using the same estradiol transdermal spray formulation as that was used in ES-01 study, daily application of two 90 μl sprays resulted in average serum estradiol concentrations in amounts comparable to currently approved transdermal estradiol products.

In NDA 21813 review, a clearance rate of 1280 L/day was used. The difference between 1280L/day and 1350 L/day is small. The calculation of in vivo delivery rate is acceptable.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence response and what is the impact of any differences in exposure on efficacy or safety response?

The intrinsic factors that may affect exposures (AUC and Cmax) and ultimately efficacy/safety are age, genetic polymorphisms in enzymes involved in estradiol metabolism, liver impairment, and renal impairment. The sponsor did not study EvaMist in special populations. Since EvaMist is for treating moderate-to-severe VMS-associated with menopause, the firm did not study the effect of age on the pharmacokinetics and exposure/response of EvaMist.

2.4 Extrinsic Factors

Patients' diet, alcohol and tobacco use may affect exposure (AUC and Cmax) and ultimately efficacy. In addition, herbal medicine and drugs that are metabolized by CYP 3A4 may cause DDI. It is unknown whether tattoo affects drug absorption and efficacy of EvaMist. Skin diseases may also affect efficacy.

2.4.1 What drug interactions may affect the PK of EvaMist?

Sponsor did not conduct drug interaction studies. However, estrogen is known to be partially metabolized by CYP3A4. Therefore inducer and inhibitor of CYP3A4 may affect the metabolism of EvaMist. FDA Guidance for Industry: Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommended Prescribing Information for Health Care Providers and Patient Labeling recommend the following to be included in the label.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens,

possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in side effects.

2.4.2 What acute effect does sunscreen application has on the absorption of EvaMist?

Table 14. Sunscreeen use study: statistical analysis of log-transformed AUC(0-24) for unadjusted estradiol serum concentrations (female subjects)

PK Parameter	Sunscreen 1 Hour Prior (C) N=20	Sunscreen 1 Hour Post (D) N=20	Control Estradiol (A) N=20	Ratio (C/A or D/A)	90% CI
ln $AUC_{(0-24)}$	750.99	--	734.72	1.02	0.87-1.20
ln $AUC_{(0-24)}$	--	655.26	734.72	0.89	0.76-1.05

Based on the 90% CI, there was a statistically significant difference between the control estradiol period and the period when sunscreen was applied 1 hr after study drug. The control estradiol is not bioequivalent to the estradiol with sunscreen applied 1 hr after.

Table 15. Sunscreeen use study: statistical analysis of log-transformed AUC(0-24) for baseline-adjusted estradiol serum concentrations (female subjects)

PK Parameter	Sunscreen 1 Hour Prior (C) N=20	Sunscreen 1 Hour Post (D) N=20	Control Estradiol (A) N=20	Ratio (C/A or D/A)	90% CI
ln $AUC_{(0-24)}$	613.56	--	600.69	1.03	0.86-1.23
ln $AUC_{(0-24)}$	--	539.75	600.69	0.90	0.76-1.08

Comments: Baseline adjustment used the average of the estradiol concentrations on Day 0 (12 hr before dosing) and Day 1 (predose). There was a lower exposure (11%) for estradiol with sunscreen 1 hr post dose as compared to no sunscreen.

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation identical to the one used for the phase 3 efficacy trial?

Yes. Confirmed with the chemist, Dr. Zhengfang Ge.

2.5.2 What is the formulation?

The to-be-marketed formulation is listed below.

4 Appendices

4.1 Proposed labeling

Please see final label in DFS if approved at time of action.

4.2 Individual Study Reviews

Please see appendix 4.2.1

4.3 Cover sheet and OCP Filing/Review Form

4.4 Attendees at my briefing which took place on June 12, 2007 (12:30 am-1:30pm):Edward Bashaw, Ahn Hae-Young, Myong-Jin Kim, Sue-Chih H. Lee, Doanh Tran, Sandhya Apparaju, Insook Kim, Tapash Ghosh

Appendix 4.2.1 **Review of Study EST-01**

This study is a Phase III multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of estradiol meter-dose transdermal spray (MDTS®) in the treatment of VMS in postmenopausal women. The study duration was Dec. 17, 2004- March 09, 2006. The study was conducted at 43 sites and involved 444 subjects with 428 subjects included in the efficacy evaluable analysis. The study is to evaluate the safety and efficacy of 1, 2, or 3 sprays of estradiol transdermal spray in the relief of moderate to severe VMS associated with menopause.

Some key inclusion criteria

1. Postmenopausal women age 35 years or older. 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels > 40IU/ml or 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy as documented by surgical records and/or pathology reports.
2. A history of frequent moderate to severe hot flushes (estimated average minimum of 8 moderate to severe hot flushes per day).
3. An adequate washout period from estrogen-containing products prior to obtaining any baseline assessments in prospective subjects who have been previous treated for postmenopausal symptoms.

Exclusion criteria: not mentioning list of drugs which are hepatic enzyme inducing drugs or hepatic enzyme inhibitors. Since this product is a topical spray, and estradiol delivered is not going through the hepatic first-pass effect, no exclusion of those who may use concomitant medication of hepatic enzyme inducing drug or hepatic enzyme inhibitors is acceptable.

Treatment Arms: At the end of the baseline evaluation period, those subjects deemed eligible to continue in the study were randomized to 1 of 6 treatment arms.

Treatment A: Estradiol transdermal spray, one 90 µL spray applied to 1 inner forearm daily for 12 weeks using a blinded applicator.

Treatment B: Estradiol transdermal spray, two 90 µL sprays applied to adjacent non-overlapping areas on 1 inner forearm daily for 12 weeks using a blinded applicator.

Treatment C: Estradiol transdermal spray, three 90 µL sprays applied to adjacent non-overlapping areas on 1 inner forearm daily for 12 weeks using a blinded applicator.

Treatment D: Placebo transdermal spray, one 90 µL spray applied to 1 inner forearm daily for 12 weeks using a blinded applicator.

Treatment E: Placebo transdermal spray, two 90 µL sprays applied to adjacent non-overlapping areas on 1 inner forearm daily for 12 weeks using a blinded applicator.

Treatment F: Placebo transdermal spray, three 90 µL sprays applied to adjacent non-overlapping areas on 1 inner forearm daily for 12 weeks using a blinded applicator.

Note: For subjects with an intact uterus, a daily dose of medroxyprogesterone acetate (MPA) 5 or 10 mg was prescribed for 2 weeks after the end of treatment to oppose any estrogen-induced endometrial proliferation that might have occurred. A follow-up visit was conducted 4 ± 1 weeks

after the end of treatment for subjects without an intact uterus or 4 ± 1 weeks after the end of MPA therapy for subjects who had an intact uterus.

Treatment administered: Doses were self-administered, with the first treatment administered in the clinic and subsequent treatments administered in the home setting. The subjects were instructed to apply 1, 2, or 3 sprays daily to the inner (ventral) surface of the forearm in the morning. If 2 or 3 sprays were employed, the additional sprays were to be applied beginning near the elbow to separate, adjacent, non-overlapping areas on the same forearm. The area of application was controlled by the cone on the applicator. For each 4-week period, subjects were instructed to apply each daily dose to the same site(s) on the same forearm until the next clinic visit. Application areas to the other forearm could be changed monthly at each clinic visit. The application site(s) should be allowed to dry for 2 minutes before covering the area with clothing and to refrain from washing the site for 30 min after each application.

Drug concentration measurement: Samples for estradiol, estrone, and estrone sulfate were collected during routine study visits at baseline (prior to treatment) at weeks 4, 8, and 12 following initiation of treatment. Samples were drawn during daytime hours, typically 2-6 hrs after the dose was administered.

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. At positive treatment effect was observed at week 2-3 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 for the 1-spray dose and this continued through week 12. The data in the following tables were adapted from Dr. Price's review.

Table 17. Reduction in the number of moderate to severe hot flushes of three doses

	3 sprays		2 sprays		1 spray	
	estradiol	placebo	estradiol	placebo	estradiol	placebo
N	76	75	76	75	76	77
Week 4	-6.64	-4.54	-7.30	-4.74	-6.26	-3.64
Week 12	-8.44	-5.32	-8.66	-6.19	-8.10	-4.76

Table 18. Reduction in severity score of moderate to severe hot flushes of three doses

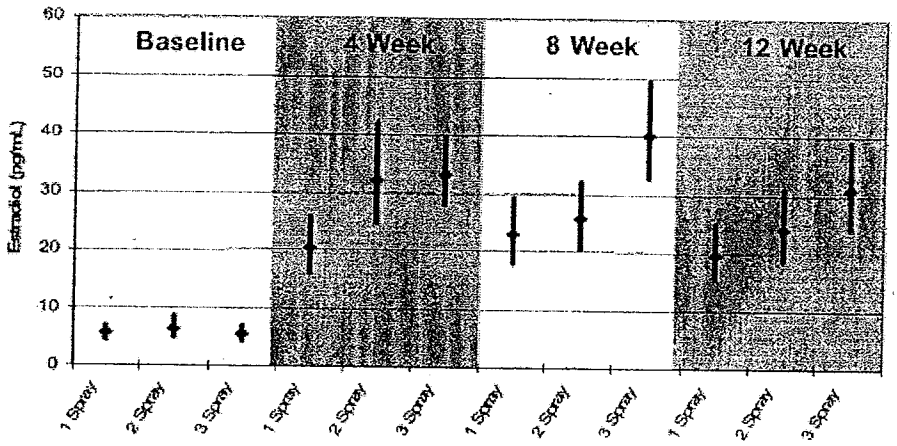
	3 sprays		2 sprays		1 spray	
	estradiol	placebo	estradiol	placebo	estradiol	placebo
N	76	75	76	75	76	77
Week 4	-0.43*	-0.13	-0.57**	-0.25	-0.47***	-0.17
Week 12	-1.07*	-0.31	-0.92**	-0.54	-1.04***	-0.26

*p<0.003 at week 4 and p<0.001 at week 12

** P < 0.0160 at week 4; p < 0.0406 at week 12

***At week 4 the p value is 0.0573; at week 12 p = <0.0001

Figure 5. Mean (95% CI)* unadjusted post-dose serum estradiol levels



Note: *: Geometric mean

Comments: In terms of reduction in severity score and hot flush frequency reduction, all three doses (1-spray, 2-spray, and 3-spray) meet the criteria of efficacy in treatint VMS.

Amendment (June-15-2007):

Table 19. Comparison of estradiol levels between subjects achieving a 50% or 75% reduction in frequency of moderate to severe hot flushes, and subjects not achieving a 50% or 75% reduction.

Responder Criteria and Time Point	Estradiol Levels (pg/mL): Values expressed as Geometric Mean (95% Confidence Interval)		p-value
	Responders	Non-responders	
50% Reduction at Week 4	30.3 (26.3- 34.8)	18.5 (12.9-26.6)	0.0012
50% Reduction at Week 12	26.5 (22.7-30.9)	16.3 (11.4-23.1)	0.0182
75% Reduction at Week 4	30.5 (25.7-36.2)	23.6 (19.1-29.2)	0.037
75% Reduction at Week 12	27.7 (23.1-33.2)	19.4 (15.5-24.4)	0.034

Table 20. Comparison of estradiol treatment on change in vasomotor score and night sweat score from baseline to week 12, ITT/Safety population.

Domain	Category	Estradiol 3-Spray	Estradiol 2-Spray	Estradiol 1-Spray
Vasomotor Score (Q 19-20)	Mean (SD)	-3.44 (1.76)	-2.72 (1.86)	-2.62 (2.18)
	p-value*		<0.0001	<0.0001
Hot Flush Score (Q 19)	Mean (SD)	-1.68 (0.86)	-1.30 (0.96)	-1.34 (1.08)
	p-value*		<0.0001	<0.0001
Night Sweats Score (Q 20)	Mean (SD)	-1.75 (1.02)	-1.42 (1.06)	-1.28 (1.19)
	p-value*		<0.0001	<0.0001

*Cochran-Mantel_Haenszel chi-square row mean-score test vs 3-spray treatment

Comments: The above tables shows that a higher estradiol exposure in those who showed 75% reduction in hot flush frequency, and that the 3-spray groups had statistically significant higher reduction in frequency and severity scores than the 2-spray and 1-spray groups.

Levels of sex hormone binding globulin

Sex hormone binding globulin assays were done at two visits, visit 2 (baseline) and visit 5 (week 12). For the estradiol-3 sprays group, 45 patients at visit 2 and 38 patients at visit 5 were monitored. For the placebo-3 sprays group, 43 patients at visit 2 and 39 patients at visit 5 were monitored. Therefore, the number of subjects with paired data was 38 and 39 for the estradiol-3 sprays and the placebo-3 sprays groups, respectively.

Table 21. SHBG levels in subjects in the 3-spray dose group, ITT/Safety population

	Estradiol 3-spray	Placebo 3-spray
	Week 12	Week 12
N	38	39
Mean (SD) (nmol/L)	53.8 (24.67)	66.1 (33.29)
Median	48.9	64
Baseline	46.2	63.2
% change from baseline	16.9%	5.7%

Table 22. Change from baseline in SHBG levels in subjects in the 3-spary dose group, ITT/safety population.

	Estradiol 3-spray	Placebo 3-spray
N	38	39
Mean (SD) (nmol/L)	7.8 (11.53)	3.3 (14.57)
p-value**	0.0002	0.1802
p-value***	0.1433	

*n=number of subjects with paired data
** Test for significant change from baseline within group using a paired t-test
*** test for treatment difference in change from baseline using t-test.

Comments: The placebo-treated group had higher baseline level than the estradiol-treated group (mean (SD): 49.1(27.27) nmol/L versus 63.8 (31.17) nmole/L). The percent change from baseline of SHBG was twice as much higher in the Estradiol-treated group than the placebo-treated group. However, the percent change from the estradiol-treated group is within the range of those observed in other NDAs, such as 21-813(Elestrin (gel))

Appendix 4.2.2 Review of Study EST-02

The formulation studied in EST02 was estradiol 1.7% MDTS, octisalate — in — ethanol USP and same as that used in phase 3 clinical trial (EST-01). The MDTS delivered 90 µl per spray. b(4)

This is a single-center, randomized, open-label, parallel group study in which 72 healthy naturally or surgically postmenopausal women, aged 40 to 65 years, were randomly assigned to receive one of three dose levels (24 subjects per treatment) of estradiol metered-dose transdermal spray (MDTS) applied to the inner forearm of the same arm once daily for 14 days. The three treatments-A, B, C-were one, two, and three 90 µl sprays, respectively, of estradiol 1.7% MDTS. In addition to the study drug treatments, subjects with an intact uterus also took 5 mg of medroxyprogesterone acetate (MPA) daily on Days 22-35 to mitigate the possible increased risk of endometrial hyperplasia and endometrial adenocarcinoma resulting from unopposed estrogen therapy.

The objective of the study is to determine the steady-state pharmacokinetic parameters of estradiol metered-dose transdermal spray (MDTS) applied to the forearm of healthy postmenopausal women.

Key inclusion criteria are
1, serum estradiol levels less than 25 pg/ml and at least one of the following:
* At least 12 months of spontaneous amenorrhea
* At least 6 months of amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/ml
* At least 6 weeks post-surgery for bilateral oophorectomy with or without hysterectomy.

2. An adequate washout period prior to obtaining any baseline assessments in women who had been previously treated for postmenopausal.

Exclusion criteria: list of drugs which are hepatic enzyme inducing drugs or oral corticosteroids, or hepatic enzyme inhibitors are adequate.

Except for one stay in the clinic (evening of Day 13 to morning of Day 15), subjects reported to the clinic each morning on Days 1-21. Treatment A (90µl), B (2X 90µl), or C (3X 90µl) was applied each morning for 14 days, and pharmacokinetic blood samples for the determination of estradiol, estrone, and estrone sulfate concentrations were collected 12 hrs pre-dose on Day 0 (baseline), predose each morning on Days 1-13, and between Days 14 and 21 at pre-dose and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 48, 72, 96, 120, 144, and 168 hours post dose. The average of the Day 0 (8:00 pm) and Day 1(8:00 am) were used for baseline correction.

PK results of estradiol and its metabolites

Figure 6. Arithmetic mean (SE) unadjusted estradiol concentration on Day 14

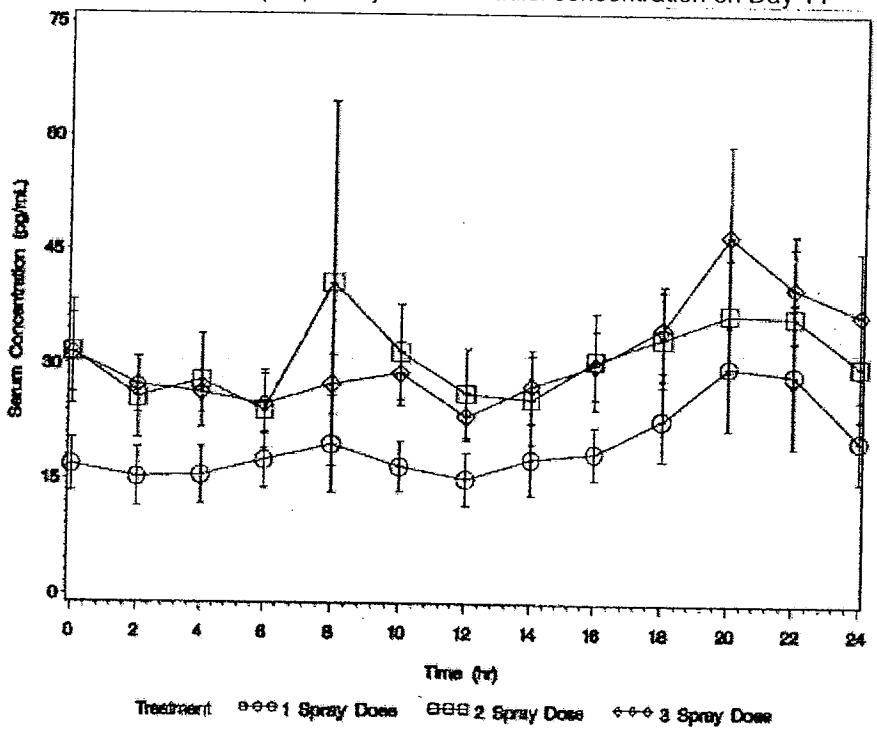


Table 23. Mean (%CV) of unadjusted serum pharmacokinetic parameters of estradiol following daily topical application of estradiol MDTS on day 14.

Parameter (units)	Treatment A 1 Spray Dose (N = 24)	Treatment B 2 Spray Dose (N = 23)	Treatment C 3 Spray Dose (N = 24)
$AUC_{(0-24)}$[1] (pg-hr/mL)	471 (49) 427 (46)	736 (43) 676 (44)	742 (30) 707 (34)
C_{max}[1] (pg/mL)	36.4 (62) 31.2 (61)	57.4 (94) 46.1 (66)	54.1(50) 48.4 (52)
T_{max}[2] (hr)	20 (0, 24)	18 (0, 24)	20 (0, 24)
C_{min}[1] (pg/mL)	11.3 (52) 10.3 (45)	18.1 (51) 16.4 (45)	19.6 (27) 18.9 (28)
T_{min}[2] (hr)	7 (0, 24)	6 (0, 24)	7 (0, 24)
C_{avg}[1] (pg/mL)	19.6 (49) 17.8 (46)	30.7 (43) 28.2 (44)	30.9 (30) 29.5 (34)
DF[1] (%)	126 (65) 107 (62)	115 (86) 95 (63)	105 (60) 92 (56)

[1] Line 1 is arithmetic mean (%CV); Line 2 is geometric mean (%CV).
[2] Median (min, max)

Table 24. Mean (%CV) of baseline-adjusted serum pharmacokinetic parameters of estradiol following daily topical application of estradiol MDTS on day 14.

Parameter (units)	Treatment A 1 Spray Dose (N = 24)	Treatment B 2 Spray Dose (N = 23)	Treatment C 3 Spray Dose (N = 24)
$AUC_{(0-24)}$[1] (pg-hr/mL)	375 (60) 325 (58)	654 (49) 584 (52)	646 (43) 623 (46)
C_{max}[1] (pg/mL)	32.4 (70) 26.4 (73)	54.0 (100) 42.1 (73)	49.8 (59) 45.1 (61)
T_{max}[2] (hr)	20 (0, 24)	18 (0, 24)	20 (0, 24)
C_{min}[1] (pg/mL)	7.3 (76) 5.9 (74)	14.6 (64) 12.6 (58)	15.8 (43) 15.3 (43)
T_{min}[2] (hr)	7 (0, 24)	6 (0, 24)	7 (0, 24)
C_{avg}[1] (pg/mL)	15.6 (60) 13.5 (58)	27.3 (49) 24.3 (52)	26.9 (43) 25.9 (46)
DF[1] (%)	160 (55) 141 (56)	132 (82) 110 (63)	120 (53) 107 (50)

[1] Line 1 is arithmetic mean (%CV); Line 2 is geometric mean (%CV).
[2] Median (min, max)

Comments: The firm concluded that dose proportionality for AUC(0-24) was inconclusive and that for Cmax was not proportional. The reviewer concluded that there is no dose proportionality..

Fig.7. Days 0-14 Mean (± SE) unadjusted pre-dose serum concentrations of estradiol versus time by treatment

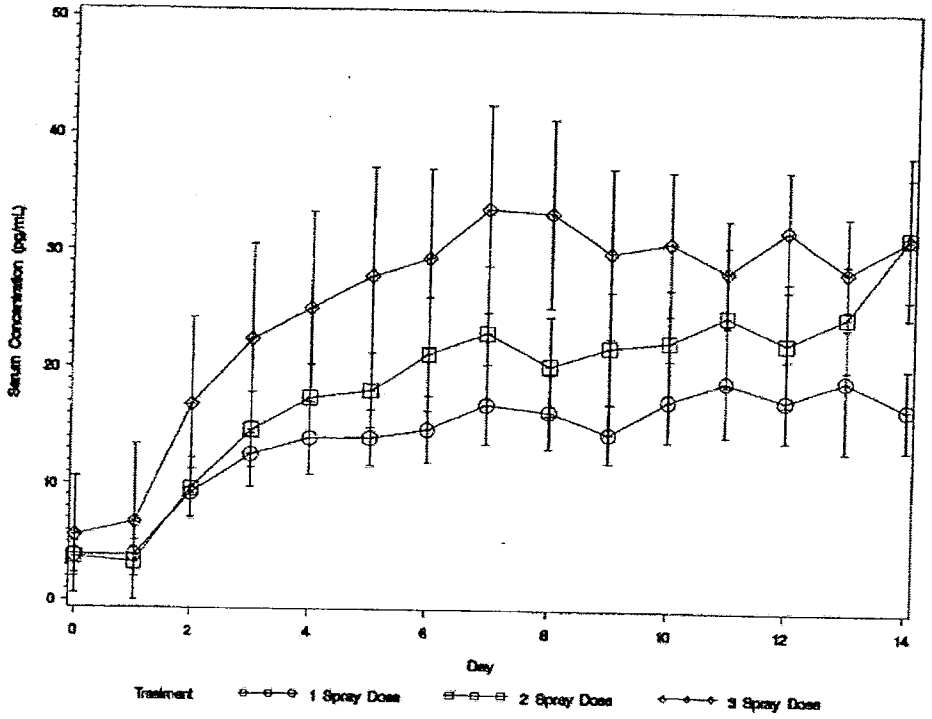


Table 25. Mean (CV%) unadjusted and baseline-adjusted estrone pharmacokinetic parameter (Day 14)

	Unadjusted			Baseline-Adjusted		
Parameter	Trt. A 1 Spray N=24	Trt. B 2 Sprays N=23	Trt. C 3 Sprays N=24	Trt. A 1 Spray N=24	Trt. B 2 Sprays N=23	Trt. C 3 Sprays N=24
$AUC_{(0-24)}$ (pg•hr/mL)[a]	886 (29) 852 (29)	1208 (26) 1168 (28)	1367 (30) 1315 (29)	411 (35) 387 (37)	735 (40) 658 (58)	900 (46) 860 (48)
C_{max} (pg/mL)[a]	49.6 (34) 47.1 (34)	60.2 (25) 58.4 (26)	71.4 (37) 67.4 (35)	29.8 (42) 27.5 (42)	40.5 (36) 37.6 (43)	51.6 (53) 48.6 (49)
T_{max} (hr)[b]	17 (0-24)	10 (0-24)	10 (0-24)	17 (0-24)	10 (0-24)	10 (0-24)[c]
C_{min} (pg/mL)[a]	30.3 (31) 29.0 (31)	41.0 (29) 39.0 (36)	46.5 (32) 44.1 (35)	10.5 (52) 9.7 (57)	21.7 (49) 20.6 (50)	27.3 (56) 24.8 (97)
T_{min} (hr)[b]	9 (0-22)	12 (0-24)	12 (0-24)	9 (0-22)	12 (0-24)	12 (0-24)
C_{avg} (pg/mL)[a]	36.9 (29) 35.5 (29)	50.3 (26) 48.7 (28)	57.0 (30) 54.8 (29)	17.1 (35) 16.1 (37)	30.6 (40) 27.4 (58)	37.5 (46) 35.8 (48)
DF (%)[a]	54 (73) 46 (60)	39 (44) 36 (39)	43 (66) 38 (55)	126 (80) 100 (72)	72 (72) 63 (52)	70 (65)[c] 70 (65)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)

[b] Median (minimum-maximum)

[c] N=23

Table 26. Mean (CV%) unadjusted and baseline-adjusted estrone sulfate pharmacokinetic parameter (Day 14)

Parameter	Unadjusted			Baseline-Adjusted		
	Trt. A 1 Spray N=24	Trt. B 2 Sprays N=23	Trt. C 3 Sprays N=24	Trt. A 1 Spray N=24	Trt. B 2 Sprays N=23	Trt. C 3 Sprays N=24
$AUC_{(0-24)}$ (pg·hr/mL)[a]	16502 (58) 13949 (67)	26515 (45) 23777 (54)	27971 (45) 25752 (42)	10567 (54) 9057 (64)	19995 (56) 16360 (83)	20958 (59) 17844 (66)
C_{max} (pg/mL)[a]	1099.8 (76) 876.5 (78)	1543.0 (47) 1368.3 (57)	1656.6 (43) 1530.4 (42)	851.4 (80) 674.7 (76)	1262.3 (54) 1083.4 (65)	1362.8 (53) 1208.1 (53)
T_{max} (hr)[b]	9 (0-24)	8 (0-24)	10 (0-24)	9 (0-24)	8 (0-24)	10 (0-24)
C_{min} (pg/mL)[a]	485.7 (58) 410.7 (67)	700.7 (54) 612.7 (58)	781.3 (47) 705.2 (50)	242.0 (66) 209.9 (71)	448.5 (86) 368.1 (98)	498.6 (73) 463.5 (62)
T_{min} (hr)[b]	19 (2-24)	20 (2-24)	18 (2-22)	19 (2-24)	20 (2-24)	18 (2-22)
C_{avg} (pg/mL)[a]	687.6 (58) 581.2 (67)	1104.8 (45) 990.7 (54)	1165.5 (45) 1073.0 (42)	440.3 (54) 377.4 (64)	833.1 (56) 681.7 (83)	873.2 (59) 743.5 (66)
DF (%)[a]	86 (70) 76 (46)	74 (41) 69 (40)	77 (34) 73 (32)	139 (80) 115 (59)	119 (94) 97 (64)	113 (53) 103 (42)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)

[b] Median (minimum-maximum)

Comments: For estrone and estrone sulfate, the increases in AUC and Cmax from 1 spray to 2 sprays, though not dose proportional, were much higher than those from 2 sprays to 3 sprays.

Appendix 4.2.3 Study EST06 review

b(4)

The formulation studied in EST06 was estradiol 1.7% MDTS, octisalate —— , ethanol USP and same as that used in phase 3 clinical trial (EST-01). The MDTS delivered 90 µl per spray.

This study was a single-center, open-label study, three 90 µl sprays of estradiol MTDS were applied daily to the inner forearm of 20 females for 18 days. For the transferability, 20 healthy male subjects participated on Days 1-3.

The objectives were to evaluate various factors that may impact estradiol absorption when applied using estradiol MDTS:

1. The possible transfer of estradiol to persons who may contact the application site of the treated individual.

2. The influence of application site washing at 1 hr post application.

3. The effect of sunscreen use at the application site at 1 hour prior to and 1 hour after application.

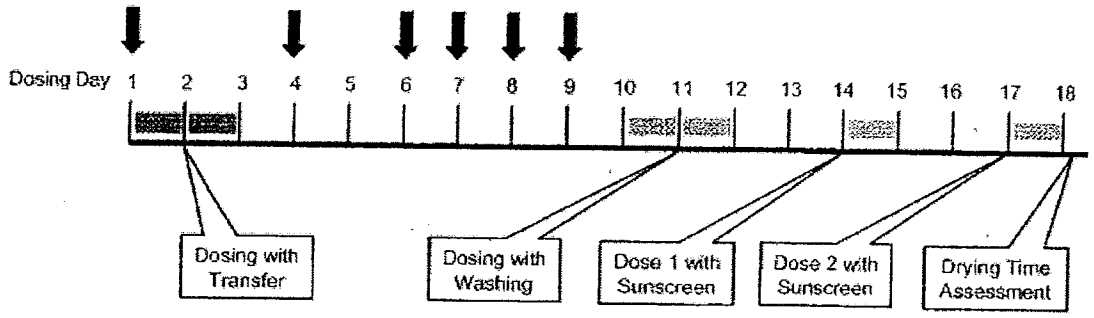
4. The time required for the estradiol MTDS spray to dry (by visual inspection).

Inclusion criteria for postmenopausal women are the same as EST-02.

Inclusion criteria for men (recipients in transfer study): 35-65 years with serum estradiol levels less than 25 pg/ml.

Exclusion criteria: list of drugs which are hepatic enzyme inducing drugs or oral corticosteroids, or hepatic enzyme inhibitors are adequate.

Study design schematic



Pre-dose blood sample for estradiol levels in women receiving study treatment.

AUC (0-24) for estradiol in women receiving study treatment. Blood samples obtained pre-dose, and 4, 8, 12, 16, 18, 20, 22, and 24 hours post dosing.

AUC (0-24) for estradiol in men contacting treated women. Blood samples obtained every 4 hours starting immediately prior to nominal exposure time.

Blood sampling times

Table 27. Serial serum concentrations of estradiol were measured, and scheduled PK blood sampling time points for each study are detailed as follows:

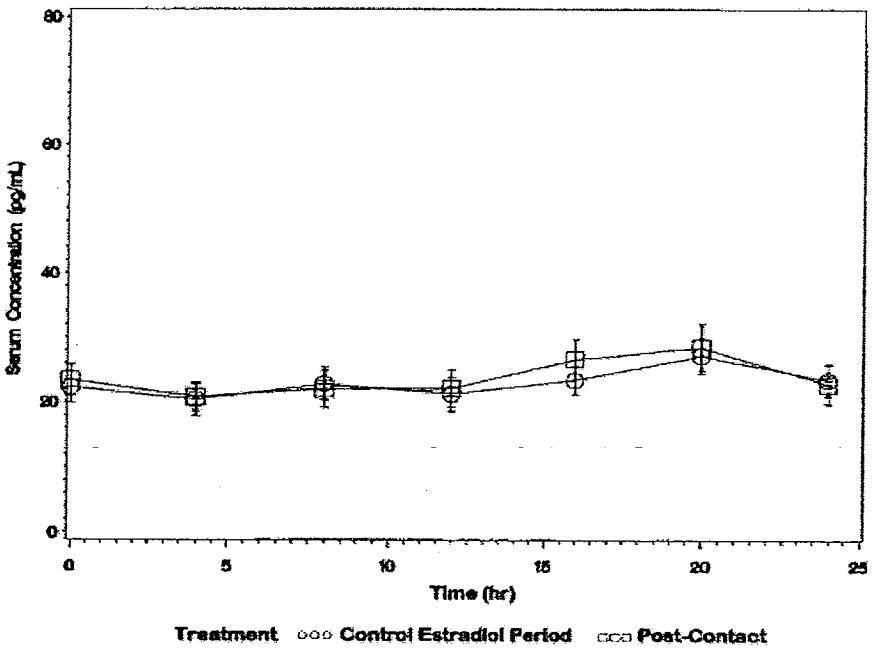
Predose baseline (female subjects)	
Day 0	Pre-dose baseline (approximately 12 hrs prior to dosing on Day 1)
Day 1	Pre-dose
Skin-to-skin transfer study (male subjects)	
Day 1 (control day)	0, 4, 8, 12, 16, 20, and 24 hrs corresponding to the time post contact on transfer day
Day 2 (transfer day)	Pre-contact, 4, 8, 12, 16, 20, and 24 hr post contact
Washing study (female subjects)	
Day 4, 6, 7, 8, 9	Pre-dose
Day 10 (control estradiol)	0, 4, 8, 12, 16, 18, 20, 22, and 24 hrs post dose

Day 11 (washing day)	0, 4, 8, 12, 16, 18, 20, 22, and 24 hrs post doe (the application site was washed at 1 hr post dosing on washing day)
Sunscreen study (female subjects)	
Day 14, period 1	0, 4, 8, 12, 16, 18, 20, 22, and 24 hrs post dose
Day 17 Period 2	0, 4, 8, 12, 16, 18, 20, 22, and 24 hrs post dose (Sunscreen was applied to the study drug application area either 1 hr prior to or 1 hr following drug application both periods)

Skin-to-skin transfer

For the skin-to-skin transfer portion of the study, approximately 1 hr after a female subject was dosed on Day 2, she held her treated inner forearm tightly (without rubbing or movement) against the inner forearm of a male subject for 5 minutes (continuous contact). Contact area was not covered with clothing or rubbed for at least 1 hr and not exposed to water for the duration of blood sampling. Blood sampling times are shown above in table 27.

Figure 8. Skin-to-skin transfer study: Mean (SEM) unadjusted estradiol serum concentrations (male subjects)



The figure above shows the mean serum concentration of estradiol-versus-time profile in control and post-contact.

Table 28. Skin-to-skin transfer study: Mean(CV%) of unadjusted estradiol pharmacokinetic parameters (male subjects)

PK Parameter	N	Control Estradiol	N	Transfer
$AUC_{(0-24)}$ (pg•hr/mL)[a]	20	550.9 (23.02%)	20	572.2 (25.30%)
		538.0 (22.27%)		556.5 (24.10%)
C_{max} (pg/mL)[a]	20	27.7 (21.14%)	20	29.6 (26.21%)
		27.2 (20.55%)		28.7 (25.09%)
T_{max} (hr)[b]	20	20.0 (0.00-24.00)	20	18.0 (16.00-20.00)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)
[b] Median (minimum-maximum)

Reviewer's comment: Minimal amount transferred.

Study days 4-9: predose-dose blood samples collected on Days 4, 5, 6, 7, 8, 9.

Effect of washing 1 hr after application

Study Days 10-13 (Washing application site study):
Study days 4-9: predose-dose blood samples collected on Days 4, 5, 6, 7, 8, 9. Predose blood sample collected Day 10-13. Daily application of three sprays of 90µl estradiol MDTS on Days 10-13. Blood samples at 4, 8, 12, 16, 18, 20, 22, and 24 hrs post dose on Day 10 were to obtain the steady state estradiol levels. The resulting steady state pharmacokinetic parameters on Day 10 were used as the control for demonstrating the effects of washing 1 hr after application and sunscreen applied 1 hr prior to or after estradiol application.

On Day 11, the application area was washed 1 hr after treatment. The washing procedure consisted of rinsing the site with 200 ml of warm water, rubbing the site with a soapy swab twice and then rinsing with a further 200 ml of warm water. The rinse water and swab were collected and a sample was analyzed for the amount of estradiol. Blood sampling times are shown above in table 27.

Table 29. Washing effect study: Mean (CV%) of unadjusted estradiol pharmacokinetic parameters (female subjects)

PK Parameter	N	Control Estradiol	N	Washing
$AUC_{(0-24)}$ (pg•hr/mL)[a]	20	869.15 (71.08%)	20	939.79 (82.36%)
		734.72 (60.60%)		756.85 (69.30%)
C_{max} (pg/mL)[a]	20	62.68 (82.15%)	20	61.01 (98.25%)
		48.91 (79.69%)		45.88 (80.64%)
T_{max} (hr)[b]	20	18.00 (0.00-24.00)	20	17.00 (0.00-22.00)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)
[b] Median (minimum-maximum)

Table 30. Washing effect study: Statistical analysis of log-transformed AUC(0-24) for unadjusted estradiol serum concentrations (female subjects).

PK Parameter	Washing (B) N=20	Control Estradiol (A) N=20	Ratio B/A	90% CI
ln $AUC_{(0-24)}$	756.85	734.72	1.03	0.92-1.15

Table 31. Washing effect study: Mean (CV%) of baseline-adjusted estradiol pharmacokinetic parameters (female subjects)

PK Parameter	N	Control Estradiol	N	Washing
$AUC_{(0-24)}$ (pg*hr/mL)[a]	19	721.44 (74.72%) 600.69 (67.24%)	19	793.77 (90.99%) 625.25 (74.01%)
C_{max} (pg/mL)[a]	19	52.05 (78.16%) 40.90 (83.27%)	19	54.61 (109.1%) 39.61 (86.87%)
T_{max} (hr)[b]	19	18.00 (0.00-24.00)	19	16.00 (0.00-22.00)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)

[b] Median (minimum-maximum)

Table 32. Washing effect study: Statistical analysis of log-transformed AUC(0-24) for baseline-adjusted estradiol serum concentrations (female subjects).

PK Parameter	Washing (B) N=19	Control Estradiol (A) N=19	Ratio B/A	90% CI
ln $AUC_{(0-24)}$	625.25	600.69	1.04	0.92-1.18

Sunscreen application

20 subjects were randomly divided into two groups with Group 1 had sunscreen applied 1 hr prior to estradiol application on Day 14 and 1 hr after estradiol application Day 17. Group 2 had sunscreen applied 1 hr after estradiol application on Day 14 and 1 hr prior to estradiol application on Day 17. A dose of 220 mg Banana Boat Faces Plus oil-free UVA and UVB Sunblock SPF 23 (non-greasy, Waterproof) was rubbed in the inner forearm for 15 seconds. After sunscreen application and estradiol MDTS dosing is complete, allow the area to dry for at least 30 minutes before covering or touching. According to the Google search, the Banana Boat faces Plus sunscreen contains octinoxate (7.5%), octisalate (5%) (sunscreen) and oxybenzone (5.75%) (sunscreen). Octinodate is octyl methoxycinnamate (OMC). Among these sunscreen ingredients, octisalate is the only absorption enhancer.

Figure 9. Sunscreen use study: mean (SEM) unadjusted estradiol serum concentrations (female subjects)

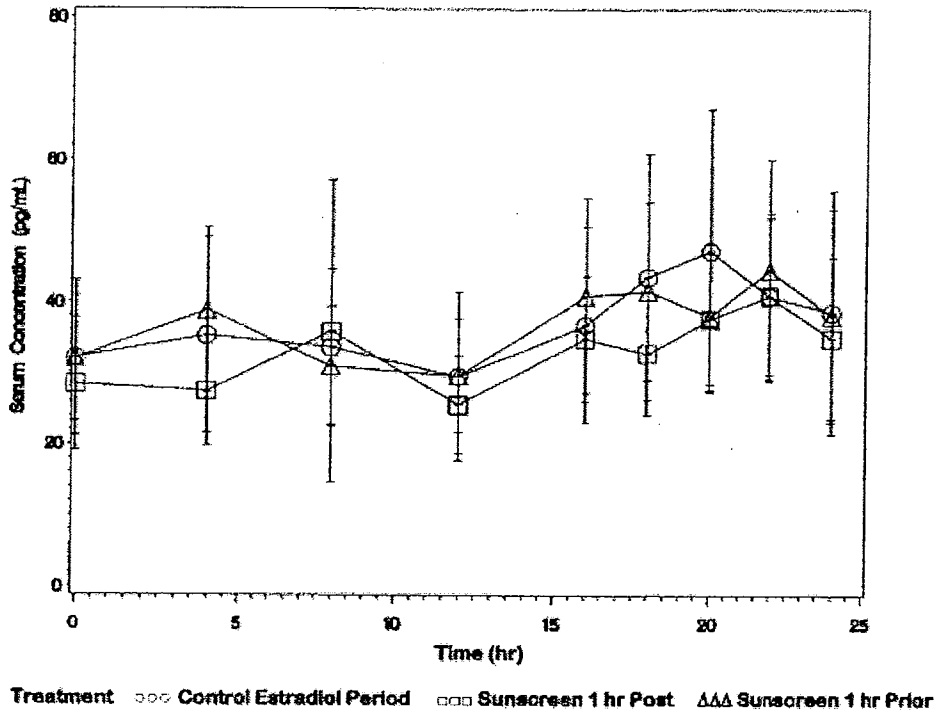


Table 33. Sunscreen use study: mean (CV%) of unadjusted estradiol pharmacokinetic parameters (female subjects)

PK Parameter	N	Control Estradiol	N	Sunscreen 1 Hr Prior	N	Sunscreen 1 Hr Post
$AUC_{(0-24)}$ (pg•hr/mL)[a]	20	869.15 (71.08%) 734.72 (60.60%)	20	869.58 (59.81%) 750.99 (59.41%)	20	773.75 (62.48%) 655.26 (64.06%)
C_{max} (pg/mL)[a]	20	62.68 (82.15%) 48.91 (79.69%)	20	56.28 (64.53%) 46.87 (69.48%)	20	55.30 (88.73%) 42.13 (85.18%)
T_{max} (hr)[b]	20	18.00 (0.00-24.00)	20	18.00 (0.00-24.00)	20	21.00 (4.00-24.00)

[a] Line 1 is arithmetic mean (CV%); Line 2 is geometric mean (CV%)

[b] Median (minimum-maximum)

Table 34. Sunscreen use study: Statistical analysis of Log-transformed AUC(0-24) for unadjusted estradiol serum concentrations (female subjects)

PK Parameter	Sunscreen 1 Hour Prior (C) N=20	Sunscreen 1 Hour Post (D) N=20	Control Estradiol (A) N=20	Ratio (C/A or D/A)	90% CI
ln $AUC_{(0-24)}$	750.99	–	734.72	1.02	0.87-1.20
ln $AUC_{(0-24)}$	–	655.26	734.72	0.89	0.76-1.05

Based on the 90% CI, there was a statistically significant difference between the control estradiol period and the period when sunscreen was applied 1 hr after study drug. The control estradiol is not bioequivalent to the estraodiol with sunscreen applied 1 hr after.

Table 35. Sunscreen use study: Statistical analysis of Log-transformed AUC(0-24) for baseline-adjusted estradiol serum concentrations (female subjects)

PK Parameter	Sunscreen 1 Hour Prior (C) N=20	Sunscreen 1 Hour Post (D) N=20	Control Estradiol (A) N=20	Ratio (C/A or D/A)	90% CI
ln $AUC_{(0-24)}$	613.56	–	600.69	1.03	0.86-1.23
ln $AUC_{(0-24)}$	–	539.75	600.69	0.90	0.76-1.08

Comments: There is a slightly lower exposure (11%) for estradiol with sunscreen 1 hr post dose as compared to no sunscreen. Based on the baseline-corrected ln AUC, the sunscreen-applied-1- hr-prior-to-EvaMist application group was bioequivalent to the control group. However, the sunscreen-applied-1-hr-post-dose group was not bioequivalent to the control group.

Drying time

On Day 18, the drying time for estradiol spray was measured by visual inspection.

Table 36. Summary of drying time for estradiol MTDS

Parameter	Drying Time (Seconds) Spray 1 N=20	Spray 2 N=20	Spray 3 N=20	Overall N=60
Mean (SD)	95.0 (53.79)	81.3 (34.27)	78.3 (38.53)	84.9 (42.92)
Median	70	67	65	67
Minimum-maximum	31-242	38-186	30-152	30-242

Comments: It is unknown why the drying for the subsequent sprays took less time.

Appendix 4.2.4 Review of Study FHRT 0001

This is a pharmacokinetic study to assess the comparative bioavailability of 17-ß-estradiol from metered-dose transdermal sprays (MDTS) and Estraderm 50 patches in postmenopausal women. The study was a single-center, three-treatment, randomized open-label crossover study. PK parameters were compared between test and reference products using standard bioequivalence testing methodology.

b(4)

This study consisted of three treatments with one treatment used a formulation [redacted] which contained an absorption enhancer different from that in the final to-be-marketed formulation. Therefore, the result of this treatment arm will not be discussed here. The results of the two treatments for comparing the formulation related to the to-be-marketed formulation and Novartis' Estraderm transdermal patch will be presented below.

Treatment A: Estraderm 50 patches (B.N.: S90493 C Exp: 07 2001). The patches were manufactured by Novaris Pharma Ag., Switzerland. The patch contains 4 mg of 17-ß-estradiol and with a nominal in vivo release rate of 50µg/24 hrs from an area of 10 cm2. Application site:abdomen. An Estraderm 50 patch was applied for 3 days after which it was removed and replaced by a new patch for another 3 days. The patches were applied to two different sites on the abdomen.

Treatment B: An estradiol MDTS containing [redacted]
— The dose applied was 182 µl sprayed over approximately 48 cm2 corresponding to a nominal estradiol dose of 1.82 mg per day. The sprays were applied as two separate sprays (one spray of 91 µl to each ventral forearm) daily for 6 days.

b(4)

Key inclusion criteria: Healthy postmenopausal women with serum estradiol levels less than 20 pg/ml, and at least 12 months amenorrhea or 6 amenorrhea and FSH levels greater than 50mIU/ml.

Exclusion criteria: women who were using hepatic enzyme inducing drugs. Since this product is a topical spray and the study is a comparative BA study, and estradiol delivered is not going through the hepatic first-pass effect, no exclusion of those who may use concomitant medication of hepatic enzyme inducing drug is acceptable.

Each treatment was applied over a 6-day period. There was a three-day wash-out period between each treatment period, therefore dose administration took place over a 24 day period. Blood samplings began on day 4 and ended on day 7 (totally 72 hrs). PK results are summarized below.

Table 37. Comparison of pharmacokinetic parameters of estradiol and estrone.

	Estradiol		Estrone	
	Treatment A (n=9)	Treatment B (n=9)	Treatment A (n=9)	Treatment B (n=9)
AUC0-72 hrs	3372	3007	3856	4640
Cavg	47.4	47.8	54.2	60.4
Cmax	74.9	88.5	68.4	83.2
Cmin	21.8	21.9	36.0	46.3
Tmax	40	6	45	20

Note: Non-baseline corrected data.

Comparisons of concentration-time profiles of estradiol and estrone between MTDS and Estraderm 50 are represented below in A and B, respectively.

Figure 10. A.

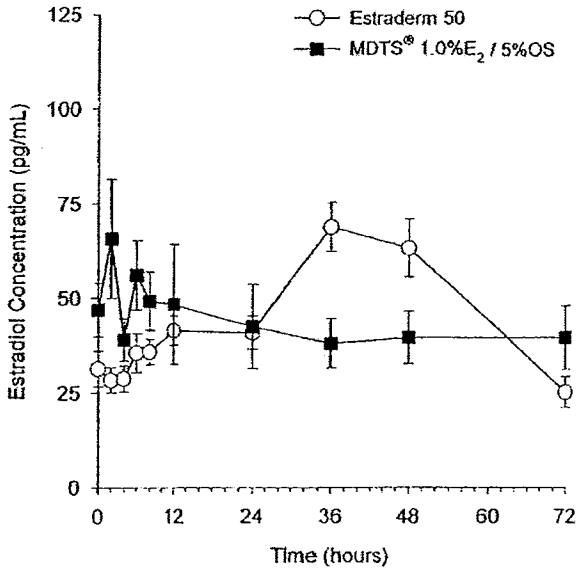
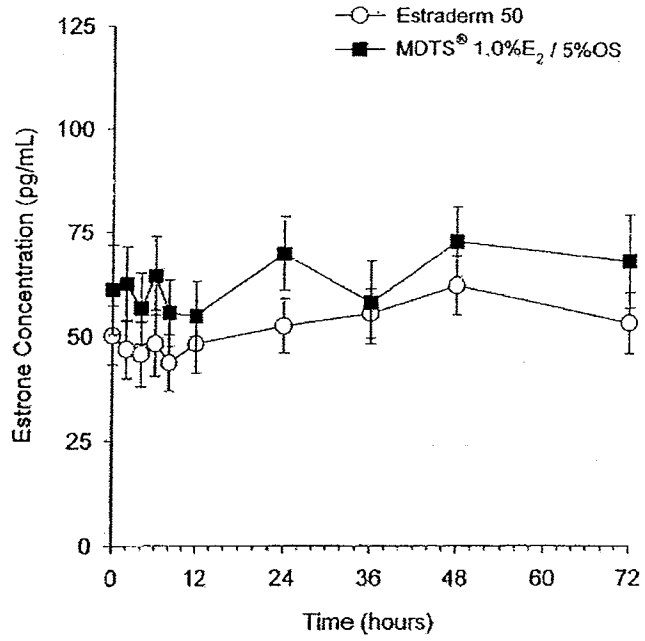


Figure 11.B.



Statistical evaluation: The 90% CI of the ratio between two treatments were 0.68-1.03 or AUC0-72 and 0.86-1.29 for Cmax.

Comments: Treatments A and B are not bioequivalent. However, this study is an exploratory dose finding study. Failure to meet bioequivalence is not crucial.

Appendix 4.2.5 Review of Study FHRT 0005

This study was a single-centre, randomized, two-way, balanced, open label, cross-over pharmacokinetic study in healthy postmenopausal women. Subjects were randomly assigned to a treatment sequence of either AB or BA according to the randomization schedule. Period I was July 16-27, 2001 and Period II August 13-24, 2001.Application site was inner arm.

Objectives of this study are to determine 1) effect of washing the application site on bioavailability, 2) single- versus multiple-dose pharmacokinetics, 3) pharmacokinetic linearity for the doses from 50 µg to 100 µg, and achievement of steady state at both doses, and 4) the time to return to baseline after dosing stops.

In this study, the formulation studied was [redacted] with each spray delivering 70µl. A dose of 4 sprays (280 µl) delivering 100 µg delivered in vivo was studied. b(4)

Key inclusion criteria: over 18 years of age. Female who has serum levels of estradiol less than 25 pg/ml and at least one of the following: 12 months spontaneous amenorrhea or; 6 months amenorrhea with serum FSH more than 50 mIU/ml or; has been on HRT for at least 5 years and is over 55 years of age. For patients already receiving hormone replacement treatment, medication had to be discontinued for at least 1 week prior to screening and at least four weeks before receiving the study treatment and for the duration of the study.

Key exclusion criteria: The list of drugs, which are hepatic enzyme inducing drugs or oral corticosteriods, are adequate. Since this product is a topical spray, and estradiol delivered is not going through the hepatic first-pass effect, no exclusion of those who may use concomitant medication of hepatic enzyme inhibitors is acceptable.

Treatment A: An estimated in vivo 100 µg dose of Estradiol MDTS (4 sprays) on day 1 followed 30 minutes later by washing the dose application site. Daily application delivers an estimated in vivo 50 µg dose of Estradiol MDTS on Days 3-8. All doses were applied to the same inner arm throughout the treatment period.

Treatment B: An estimated in vivo 100 µg dose of Estradiol MDTS (4 sprays) on day 1 without washing of the dose application site. On Days 3-8, estradiol transdermal spray (was applied once daily to the ventral forearm. All doses were applied to the same inner arm throughout the treatment period.

Washing procedure: The washing procedure consisted of rinsing the site with 200 ml of warm water, rubbing the site with a soapy swab and then rinsing with a further 200 ml of warm water. The rinse water and swab were collected and a sample was analyzed for the amount of estradiol. The combined average concentration (period I and period II) of estradiol measured in the washing material was 0.15µg/ml. Based on the volume and concentration, the amount in the wasing materials was 5.4% of the applied dose.

Demographics of subjects
All 26 subjects were female Caucasians. The means of age, weight, and height were 61 years, 72.15kg and 161.8 cm.

Table 38. Effect of washing on the uncorrected pharmacokinetic of estradiol.(n=25)

Parameter	Treatment A (100 µg estradiol followed by	Treatment B (100 µg estradiol with no

		washing)	washing)
Day 1	AUC (0-48) pg * hr/ml	1235.54 ± 1082.5	1057.89 ± 475.68
	Cmax Pg/ml	96.6 ± 177	58.9 ± 44.8
	AUC (0-48) Ratio Estradiol/estrone	0.81 ± 0.54	0.72 ± 0.36

Table 39. Statistical summary of the effect of washing the dose application site on Day 1

Parameter		Treatment A (100 µg estradiol followed by washing)	Treatment B (100 µg estradiol with no washing)	P value	Mean ratio (%) (A/B X 100) (90%CI)
Baseline-corrected log-transformed estradiol data (n=25)					
Day 1	AUC (0-48) pg * hr/ml	717.3	600.88	0.3285	119.4 (88.1-161.8)
	Cmax Pg/ml	50.4	39.2	0.1096	128.8 (99.2-167.2)
Baseline-corrected log-transformed estrone data (n=25)					
Day 1	AUC (0-48) pg * hr/ml	519.4	518.32	0.9842	100.2 (82.3-118.1)
	Cmax Pg/ml	26.0	28.2	0.3877	92.2 (76.9-107.4)

The Tmax from treatment A had an arithmetic mean of 24.44 hr while that from treatment B 21.05 hr.

Comments: Washing seemed to increase the AUC and Cmax of estradiol. According to the P-value, there were no statistical differences for AUC, Cmax and Tmax between washing and no washing. However, the bioequivalence analysis based on 90% CI, there is no bioequivalence between washing and no washing. Since approximately 5% of estradiol was detected in the washing material, the most likely explanation for higher AUC and Cmax from washing is that the washing procedure of using warm water and scrubbing might have actually facilitated absorption of estradiol on the skin through higher temperature and greater exposed skin area.

Table 40. The uncorrected steady state dose/exposure relationship of estradiol.(n=25) on day 8.

	Parameter	Treatment A (140 µl as 2 sprays) (50 µg estradiol)	Treatment B (280 µl as 4 sprays) (100 µg estradiol)
Day3 -Day 8 once a day application	AUC (0-24) pg * hr/ml	740.76 ± 359.84	1152.22 ± 587.3
	Cmax Pg/ml	70.7±50.3	115 ± 105
	Cmin Pg/ml	15.2 ± 7.04	23.1 ± 9.25
	Cavg Pg/ml	30.9 ± 15.0	48.0 ± 24.5

* Spray applications began on Day 3 and plasma levels were measured on Day 8.

Table 41. Statistical comparison of single-versus multiple-dose uncorrected pharmacokinetics of estradiol

Parameter	Treatment B (day 1)	Treatment B (day 1)	Mean ratio (%) Day 1/Day 8
AUC pg-hr/ml	1057.89 ± 475.68	1152.22 ± 587.3	0.92
Cmax (pg/ml)	58.9 ± 44.8	115 ± 105	0.512

Comments: The steady state pharmacokinetic parameters of estradiol seemed to increase almost proportionally with dose when two doses of 50 μg and 100 μg were compared. Tmax from treatment A was 21.1 hrs and that from treatment B 18 hrs. The steady state Cmax was much higher than that from single-dose, though AUC did not accumulate extensively. The firm conducted the blood sampling for 24 hrs after the 8-day dosing and the blood concentration at 24-hr after dosing was much higher than the baseline.

Appendix 4.2.6 Review of Study FHRT 06

A single centre, open label pharmacokinetic study in healthy postmenopausal women was conducted using a randomized, three-way, crossover design. The objective is to compare the effect of different application sites and formulations on the steady state pharmacokinetics of estradiol, and its metabolite estrone, following application of an Estradiol MDTS in healthy postmenopausal women.

Three study periods of 8 days, each period separated by a 6 day washout: Period I: 15 July-23 July, 2002, Period II: 29 July-06 August, 2002, Period III: 12 August -20 August, 2002. Twelve healthy postmenopausal females were enrolled, 11 of whom completed the study. Subjects were randomly assigned to a treatment sequence of any of ABC, ACB, BAC, BCA, CAB, and CBA according to a randomization schedule. The demographic characteristic of the subjects: all Caucasian, age, 58 ± 4.9, weight 73.97± 16.7, height 163.7 ± 4.4.

Key inclusion criteria: over 45 years of age. Female who has serum levels of 17ß-estradiol less than 25 pg/ml and at least one of the following: 12 months spontaneous amenorrhea; 6 molnths amenorrhea with serum FSH levels more than 50 mIU/ml; or has been on HDT for at least 5 years and is over 55 years of age. For those who already receiving hormone replacement treatment, medication has to be discontinued for at least one week prior to screening, at least 4 weeks before receiving the study treatment and for the duration of the study.

Exclusion criteria: list of drugs which are hepatic enzyme inducing drugs or oral corticosteriolds, or hepatic enzyme inhibitors are adequate.

Treatment A: Estradiol MDTS containing [redacted] Two
90 μl sprays were applied once daily to adjacent sites on the ventral forearm for 7 days.

Treatment B: Estradiol MDTS containing [redacted] Two
90 μl sprays were applied once daily to adjacent sites on the ventral forearm for 7 days.

b(4)

Treatment C: Estradiol MDTS containing [redacted] Two
90 μl sprays were applied once daily to adjacent sites on the inner thigh for 7 days.

Blood samples were collected for determination of serum estradiol and estrone conentrations prior to dosing on Day 0, Day 1, Day 6, and Day 7, and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hrs after dosing on Day 7.

Table 42. Summary of uncorrected estradiol pharmacokinetic parameters.

Parameter	Treatment A (Estradiol MDTS — forearm) Mean ± SD	Treatment B (Estradiol MDTS 1.7% forearm) Mean ± SD	Treatment C (Estradiol MDTS 1.7% inner thigh) Mean ± SD
AUC (pg* hr /ml)	741 ± 305	826 ± 409	948 ± 578
Cmax (pg/ml)	64.1 ± 44.8	56 ± 27.5	86.2 ± 75.1
Tmax (hr)	14.03 ± 7.27	16.02 ± 7.27	19.83 ± 2.43
Cmin (pg/ml)	17.7 ± 7.8	19.4 ± 8.1	17.1 ± 7.8
Cavg (pg/ml)	30.9 ± 12.7	34.4 ± 17	39.5 ± 24
DF (%)	140 ± 110	104 ± 28	142 ± 72
Ratio AUC0-24 Estradiol/Estrone	0.77 ± 0.30	0.77 ± 0.32	0.81 ± 0.46

b(4)

Table 43. Summary of baseline-corrected estradiol pharmacokinetic parameters.

Parameter	Treatment A (Estradiol MDTS — forearm) Mean ± SD	Treatment B (Estradiol MDTS 1.7% forearm) Mean ± SD	Treatment C (Estradiol MDTS 1.7% inner thigh) Mean ± SD
AUC (pg* hr /ml)	645± 319	730 ± 428	852 ± 565
Cmax (pg/ml)	60.1 ± 44.8	52 ± 28.4	82.2 ± 74.9
Cmin (pg/ml)	13.7 ± 8.4	15.4 ± 9.1	13.1 ± 7.3
Cavg (pg/ml)	26.9 ± 13.3	30.4 ± 17.8	35.5 ± 23.5
DF (%)	172 ± 132	124 ± 31	159 ± 72
Ratio AUC0-24 Estradiol/Estrone	1.26 ± 0.59	1.17 ± 0.38	1.15 ± 0.73

b(4)

Table 44. Summary of uncorrected estrone pharmacokinetic parameters.

Parameter	Treatment A (Estradiol MDTS — forearm) Mean ± SD	Treatment B (Estradiol MDTS 1.7% forearm) Mean ± SD	Treatment C (Estradiol MDTS 1.7% inner thigh) Mean ± SD
AUC (pg* hr /ml)	983 ± 252	1077 ± 348	1209± 452
Cmax (pg/ml)	51.7 ± 12.6	58.2 ± 23.5	62.9 ± 24.6
Tmax (hr)	14.37 ± 10.11	16.94 ± 8.51	17.28 ± 8.72
Cmin (pg/ml)	31.6 ± 9.0	33.3 ± 10.3	40.3 ± 16.5
Cavg (pg/ml)	41 ± 10.5	44.9 ± 14.5	50.4 ± 18.8
DF (%)	50.6 ± 17.7	52.0 ± 24.3	44.6 ± 18.4

b(4)

Table 45. Summary of baseline-corrected estrone pharmacokinetic parameters.

Parameter	Treatment A (Estradiol MDTS — forearm) Mean ± SD	Treatment B (Estradiol MDTS 1.7% forearm) Mean ± SD	Treatment C (Estradiol MDTS 1.7% inner thigh) Mean ± SD
AUC (pg* hr /ml)	542 ± 233	635 ± 358	767± 365
Cmax (pg/ml)	33.3 ± 11.5	39.8 ± 23.6	44.5 ± 21.1
Cmin (pg/ml)	13.2 ± 10.5	14.9 ± 11.6	21.9 ± 13.4
Cavg (pg/ml)	22.6 ± 9.7	26.5 ± 14.9	32 ± 15.2
DF (%)	108 ± 72	109 ± 79	72.5 ± 32.3

b(4)

Comments:
All three treatments produced significant elevations in serum estradiol and estrone levels compared to baseline. The 1.7% formulation is the to-be-marketed formulation and resulted in slightly higher AUC, Cmin and Cavg of estradiol than the , formulation. The 1.7% had lower DF% and Cmax of estradiol than the formulation. The MDTS treatment containing 1.7% estradiol applied to the inner thigh seemed to produce higher mean serum estradiol and estrone levels than the same MDTS formulation applied to the forearm; however, the difference was not statistically significant. The AUC ratio of inner thigh treatment to inner forearm treatment was 1.17 and the Cmax ratio of inner thigh treatment to inner forearm treatment was 1.12. Based on the statistical comparison on the baseline-corrected pharmacokinetics, application to the inner thigh is not bioequivalent to application to the forearm with 90% CI of 83.2%-149% for AUC0-24 and 86.6%-189% for Cmax.

b(4)

4.4.1 Office of Clinical Pharmacology

5 *New Drug Application Filing and Review Form*

5.1.1.1.1 General Information about the Submission

	Information		Information
NDA Number	22-014	Brand Name	EvaMist
OCP Division	DCP - 3	Generic Name	Estradiol transdermal spray
Medical Division	DRUP	Drug Class	Sex hormone
OCP Reviewer	Myong-Jin Kim	Indication(s)	Treatment of moderate to severe vasomotor symptoms
OCP Team Leader	Myong-Jin Kim	Dosage Form	Transdermal spray
Division Director	E. Dennis Bashaw	Dosing Regimen	Once daily
Date of Submission	September 29, 2006	Route of Administration	Transdermal
Estimated Due Date of OCP Review		Sponsor	Vivus, Inc.
PDUFA Due Date	July 29, 2007	Priority Classification	S
5.1.1.2 Division Due Date			

5.1.1.2.1.1.1.1 Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

5.2 Healthy Volunteers-				
single dose:				
multiple dose:				
5.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies				
5.2.1.1.1.1				
5.2.1.1.1.2 Filability and QBR comments				

5.2.1.2	"X" if yes	5.2.1.2.1.1.1.1.1 Comments
5.2.1.3 **Application filable ?**	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
5.2.1.4 **Comments sent to firm ?** 5.2.1.5		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Myong-Jin Kim**	
Secondary reviewer Signature and Date		

2) EST-02: A Study to Assess the Steady-State PK Parameters of Estradiol MDTS® Applied to the Forearm of Healthy Postmenopausal Women

- To assess the steady-state PK profile (14 day) of one, two, or three 90 µL/sprays daily when applied to the inner surface of the forearm of 72 healthy postmenopausal women
- PK parameters were calculated using both uncorrected and baseline-corrected values. Baseline-corrected values were calculated by subtracting the mean of the two baseline values (Days 0 and 1)

3) EST-06: A Study to Determine the Effects of Skin-to-Skin Contact, application Site Washing and Sunscreen Use with Administration of Estradiol MDTS

- Assessed external factors that could affect estradiol absorption from the transdermal spray in 20 healthy postmenopausal women. These included (1) potential transfer of estradiol to persons who may come into contact with the site of application (5 minutes of continuous forearm-to-forearm contact 1 hour after the application of EvaMist); (2) influence of washing the site of application after treatment (washed 1 hour after the application of EvaMist); (3) effect of sunscreen on estradiol absorption (sunscreen was applied 1 hour before or 1 hour after the application of EvaMist); and (4) the time required for the application site to dry

Bioavailability (BA) Studies:

3) **FHRT-0001**: A PK Study to Assess the Comparative BA of 17-beta Estradiol from MDTS and Estraderm 50® Patches in Postmenopausal Women

- A formulation of [redacted] b(4)
- Estradiol concentrations were comparable to a marketed estradiol patch (Estraderm®)
- The [redacted] atio of estradiol:octisalate was fixed for the formulation development

4) **FHRT-0002**: A PK Phase I Study to Assess the Comparative BA of 17-beta Estradiol from MDTS and Estraderm 50® Patches in Healthy Postmenopausal women

- [redacted] b(4)
- Estradiol concentrations were similar to those provided by the Estraderm® (unreliable results due to contamination error at the clinical site)

5) **FHRT-0005**: A Study to Determine the Linearity of the PK and the Effect of Washing the Application Site on the BA of Estradiol from an Estradiol MDTS®

- [redacted] b(4)
- Dose proportionality was observed between 2 and 4 sprays; no significant effect of washing the application site 30 min after application on the extent of absorption of estradiol
- Estradiol concentrations were less than the desired [redacted], so the volume delivered was increased to 91 µL/spray b(4)

6) **FHRT-09**: A Phase I Study to Compare the Steady-State PK of Estradiol Following Application to the Abdomen of an Estradiol MDTS and Estraderm 50® Patches in Healthy Postmenopausal Women

- [redacted] b(4)
- Estradiol absorption was lower when it was applied to the abdomen than in previous studies where it was applied to the forearm

- Estradiol concentrations were still below the desired [redacted] so the concentration of estradiol in the formulation was increased to 1.7% and the concentration of octisalate was increased in parallel to maintain the ratio b(4)

7) **FHRT-06**: A PK Phase I Study to Assess the Effect of Different Application Sites and Formulations, on the Relative BA and PK of Estradiol from a Metered Dose Transdermal System (MDTS)

- Estradiol concentrations attained with a [redacted] formulation were in the [redacted] range b(4)
- This formulation was chose as the final formulation

Recommendation:

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-014 is fileable.

Pending issues:

- During the Pre-NDA meeting on June 28, 2006, the Division requested that the individual subject clinical pharmacology data from the studies using the final product conducted by VIVUS be submitted electronically.
- In addition, the Division requested that you provide the available sex hormone binding globulin data from different doses other than 3 sprays/day.

_____ _____

Myong-Jin Kim, Pharm.D., Team Leader Date

_____ _____

E. Dennis Bashaw, Pharm.D., Division Director Date

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/s/

Jane Bai
7/9/2007 08:07:43 AM
BIOPHARMACEUTICS

Myong-Jin Kim
7/10/2007 06:02:41 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-014**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**Sept. 29, 2006**
PRODUCT:	**Evamist**
INTENDED CLINICAL POPULATION:	**women with menopausal symptoms**
SPONSOR:	**Vivus, Inc.**
DOCUMENTS REVIEWED:	**No Module 4 was submitted; CTD summaries reviewed**
REVIEW DIVISION:	**Division of Reproductive and Urologic Products (HFD-580)**
PHARM/TOX REVIEWER:	**Leslie C. McKinney, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR (Acting):	**Scott Monroe, MD**
PROJECT MANAGER:	**Kassandra Sherrod, R. Ph.**

Date of review submission to Division File System (DFS): May 21, 2007

Executive Summary

I. Recommendations

A. Recommendation on approvability
NDA 22-014 (EvaMist®, estradiol transdermal spray) has been submitted by Vivus, Inc. for the treatment of moderate to severe vasomotor symptoms associated with menopause. It is administered as a transdermal spray containing the active ingredient estradiol at 1.7% w/v. One 90 uL spray contains 1.53 mg estradiol, which delivers ~21 µg estradiol to the systemic circulation. Up to three sprays may be applied daily to nonoverlapping 20 cm^2 areas of forearm skin. From a Pharm/Tox perspective, this NDA may be approved.

B. Recommendation for nonclinical studies
In an advice letter dated January 20, 2006, DRUP indicated to Vivus that, based on general class safety of estrogens at the proposed doses, no nonclinical studies would be required for filing the EvaMist® NDA, and that there would be no Module 4 of the Common Technical Documents. Therefore, no new nonclinical studies were carried out in support of this NDA. There are no further Pharm/Tox recommendations for nonclinical studies.

C. Recommendations on labeling
There are no Pharm/Tox recommendations for changes in the proposed labeling for EvaMist®.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
There were no nonclinical studies submitted in support of this application. Estradiol is a well-studied, naturally occurring steroid hormone that has been extensively characterized in many nonclinical species and in humans. Estrogens as a class show minimal acute toxicity, even at high doses, and chronic use is well tolerated. Because its pharmacological effects and toxicities are considered general knowledge, further studies in animals were deemed unnecessary to define the safety profile of estradiol.

B. Pharmacologic activity
Estradiol is an estrogen that regulates fertility and reproduction in humans and in mammalian nonclinical species. The estradiol in EvaMist® is chemically identical to naturally occurring estradiol, and because it is administered transdermally, it avoids hepatic first-pass metabolism. The administered dose yields physiological levels of circulating hormone that binds to estrogen receptors in various target tissues and yields normal pharmacological effects.

C. Nonclinical safety issues relevant to clinical use
Literature reviews and toxicology database searches were conducted to assess the safety of the excipients and impurities present in the EvaMist® drug product. None of the excipients or impurities were present at levels that pose a toxicological concern. There are no nonclinical safety issues relevant to clinical use.

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/s/

Leslie McKinney
5/21/2007 12:17:21 PM
PHARMACOLOGIST

Lynnda Reid
5/21/2007 12:32:23 PM
PHARMACOLOGIST