CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

CROSS DISCIPLINE TEAM LEADER REVIEW

Evamist™ (estradiol transdermal spray)
Team Leader Review

NDA:	**22014**
Drug:	**Evamist™ (estradiol transdermal spray)**
Indications:	**Treatment of moderate-to-severe vasomotor symptoms due to the menopause**
Dosage/Form/Route:	**1.53mg Estradiol administered as 1, 2 or 3 transdermal sprays**
Applicant:	**VIVUS, INC.**
Original Submission Receipt Date:	**September 29, 2006**
Primary Review Completion date:	**July 26, 2007**
Date of Final Memorandum:	**July 27, 2007**

Executive Summary:

A single Phase 3 study, EST-01, was submitted in support of efficacy and safety of estradiol transdermal spray for the treatment of moderate to severe vasomotor symptoms. The safety base was composed of 556 subjects and the safety profile of each of the 1-, 2-, and 3-90 µL estradiol transdermal spray doses was acceptable. Results of Study EST-01 demonstrated that relative to treatment with placebo, treatment with each of the 1-, 2- and 3-90 µL estradiol transdermal spray doses resulted in both clinically and statistically significant reductions in frequency and statistically significant reductions in severity of vasomotor symptoms at Week 4 which was maintained through Week 12 and, thus, met the criteria for efficacy as stated in the January 2003 Draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (to be referred to in this review as the Draft HT Clinical Trial Guidance).

Although efficacy was demonstrated in all three estradiol transdermal spray dosage groups, the study results show little clinical difference between the 2-spray dose and the 3-spray dose. This is consistent with the pharmacokinctic data which showed little difference in the C_{max} and C_{aver} between 2-spray and 3-spray dosages as measured at day 14 of the primary clinical study. However, there was a great deal of variability in both the symptom relief data and the pharmacokinetic data. Also noted is the design of the spray cone delivery system and potential variability of delivery to the forearm of women with varying forearm surface areas. In women with small forearm surface areas, part of the delivered spray is potentially wasted external to the arm without contact to actual surface area. This reviewer believes that this potential variability in product delivery may account for the high degree of variability in the symptom relief data and the pharmacokinetic data and may account for the lack of true dose proportionality in the results. Nevertheless, treatment with all three of the dosages demonstrated efficacious and safe results. It is this reviewer's belief that even though the mean treatment data did

not demonstrate better results with the 3-spray dose than with the 2-spray dose in the primary clinical trial, in actual market use, some individual women may receive benefit from the 3- spray dose beyond that of the 2-sprays dose and, thus, all three efficacious and safe doses should be available to titrate the dosage if necessary.

Based on substantial evidence of efficacy and safety, this reviewer recommends that each of the 1-, 2-, and 3-90 µL estradiol transdermal spray doses be approved for the indication of treatment of the moderate to severe vasomotor symptoms due to the menopause.

Background and Regulatory History

A pre-IND meeting was held with the Sponsor, Acrux (FemPharm Pty.Ltd), on August3, 2000. IND 62,602 for estradiol metered dose transdermal system was opened with submission of a Phase 2 comparative bioavailability study of 50 and 100 µg/day doses on May 7, 2001. On April 22, 2003, an "End-of-Phase 2" (EOP2) Meeting was held to discuss plans for Phase 3 development. At that meeting the Division of Reproductive and Urologic Products (Division) recommended that Acrux Ltd follow recommendations in the January 2003 Draft HT Clinical Trial Guidance with respect to trial design and demonstration of efficacy for their proposed Phase 3 study(s). The Division also recommended the use of endometrial biopsies to assess endometrial safety at baseline and end-of-study.

On March 12, 2004 VIVUS, INC notified the Agency that effective March 2, 2004 sponsorship of IND 61602 was transferred from Acrux (FemPharm Pty.Ltd) to VIVUS INC.

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

- A single Phase 3 trial was acceptable.
- The Sponsor should use the clinical definitions of mild, moderate, and severe to describe the severity of vasomotor symptoms.
- The sample size should be increased to approximately 74 subjects per treatment group to account for potential dropouts.
- The study should identify the lowest effective doses and exposure for estrogen-related compounds. The sponsor added a third dosing group (3-spray) to the original protocol to ensure that adequate systemic exposure was achieved.
- The Agency agreed to the inclusion/exclusion criteria recommended by the sponsor for Phase 3.
- The primary endpoints were the mean change in frequency of moderate to severe vasomotor symptoms (VMS) from baseline to week 4 and to week 12

and the mean change in severity of moderate to severe VMS from baseline to week 4 and to week 12. Descriptive analyses were performed for the age subgroups of less than 50 years of age, 50-59 years of age, and greater than 59 years of age

- Incomplete diary primary endpoints would be handled by imputation with the last observation carried forward for the ITT/safety and modified ITT populations.

The SAP was submitted on November 10, 2005; the initial response from the Agency was dated January 20, 2006. The Agency sought clarification of the statistical adjustment procedure being applied for the control of Type I error relating to the testing of the three dose arms. A revised SAP was submitted on February 9, 2006 and a teleconference to discuss the SAP was held on April 13, 2006. Agreement was reached between VIVUS and the Agency on the SAP. The final SAP was submitted on April 26, 2006 before the database lock and unblinding of any data occurred.

Recommendation on the NDA content and filing strategy were proposed by VIVUS in a correspondence on November 10, 2005 and agreed to by the Agency on January 20, 2006. A pre-NDA Chemistry, Manufacturing and Control (CMC) meeting was held on April 26, 2006. Agreement between VIVUS and the Agency on CMC issues was reached at this meeting.

A pre-NDA clinical meeting was held on June 28, 2006 and agreements were made between the Agency and VIVUS. The major agreements included:

- The Agency's acceptance of the plans for summaries of Biopharmaceutics and Clinical Pharmacology, Clinical Efficacy and Clinical Safety in the submission
- Concurrence that Evamist™ meets the requirements for exclusion from pediatric study requirements
- The Agency's request for subgroup analyzes on BMI; additional secondary supportive information on responder analyzes at 75%.

NDA 22014 was received by the Agency on September 29, 2007 and administratively filed on November 28, 2006.

Clinical

Efficacy

Study EST-01

A single Phase 3 Study, EST-01, was conducted in support of treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

Study EST-01 was a Phase 3 multicenter (43 sites in the US), randomized, double-blind, parallel group, and placebo-controlled trial. Subjects were screened to those who had ≥ 8 moderate-to-severe hot flushes per day at baseline consistent with the HT Clinical Trial Guidance. Seven hundred-seven (707) subjects were screen failures. Four Hundred Fifty

Eight (458) subjects were randomized to the 1-, 2- or 3-90 μL estradiol transdermal spray, or matching placebo according to the following randomization scheme: 1-estradiol transdermal spray – 77 subjects, 1-placebo transdermal spray – 77 subjects, 2-estradiol transdermal sprays – 76 subjects, 2-placebo transdermal sprays – 76 subjects, 3-estradiol transdermal sprays – 76 subjects and 3-placebo transdermal sprays – 76 subjects. Four Hundred Fifty Four (454) received at least one dose of the test material and were analyzed in the intent-to-treat population (ITT). Four randomized subjects were not treated under the protocol. Three subjects (6020126, 6370133, and 6420127) were randomized in error (1-spray, 3-spray placebo, 2-spray estradiol, respectively) and were withdrawn prior to receiving any treatment. One additional subject (6360124) 2-spray group) requested to be withdrawn prior to treatment.

Each spray was applied to adjacent non-overlapping areas on one inner forearm daily for 12 weeks.

Demographics

The majority of subjects were naturally menopausal. The mean ages (± SD) per treatment groups were 53.5 ± 6.8, 52.2 ± 6.8, 52.3 ± 5.7 in the 1, 2, and 3 transdermal estradiol spray groups, respectively, and 52.8 ± 6.9, 52.0 ± 7.0 and 52.0 ± 6.3 in the placebo 1, 2, and 3 spray treatment groups, respectively. Approximately 70% (318/545) of subjects were Caucasian, 24.4% (111/454) were Black, 3.5% (16/454) were Hispanic, 5 (1.1%) were multi-racial, and 1 each was American Indian or Alaskan Native or Other. The average BMI was 27.1± 4.5 kg/m2 and that there were no statistically significant difference between treatment groups.

VMS

Subjects maintained a daily diary of hot flush frequency and severity. The average number of moderate and severe hot flushes for each time period was calculated as:

$$\frac{\textit{Total number of moderate and severe hot flushes for 7 days}}{\textit{7days}}$$

Severity was scored as: mild, moderate and severe. The average severity of moderate to severe hot flushes for each time period was calculated as:

$$\frac{\textit{(number of moderate hot flushes for a week) x 2 + (number of severe hot flushes for a week) x 3}}{\textit{Total number of moderate and severe hot flushes for a week}}$$

The protocol-specified primary efficacy population is the ITT population, which was defined as all subjects randomized to treatment who receive at least one dose of study medication.

Missing daily frequency values were imputed by severity from daily means from non-missing values for that week as long as there are at least 4 days of non-missing data. Otherwise, the LOCF was used. For subjects terminating the study prematurely, the LOCF method was used to provide data for scheduled assessments that were missed. Missing severity values were calculated from the imputed frequency values.

The primary analysis used an analysis of covariance (ANCOVA) model with treatment, region, and treatment-by-region interaction as factors and baseline score as covariate for comparisons between each estradiol group and placebo for the change from baseline in the average number and severity of hot flushes. The results from centers were pooled on the basis of geography (N, S, E, W) and testing was done using a t-test based on the ANCOVA model.

The three pairwise comparisons of each estradiol dose to its matching placebo were made with a separate ANCOVA model run on each pairwise comparison. Statistical significance is declared at the 0.05 level for each dose comparison that includes all four co-primary endpoints. A step-down procedure was used where the 3-spray arms are compared first, then the 2-spray arms, followed by the 1-spray arms. Testing was stopped once a statistical test fails to reach significance for any of the 4 co-primary endpoints.

The primary efficacy analyses for frequency of vasomotor symptoms are shown in Table 1 [adapted from Medical Officer Review (MOR) Tables 5, 7 and 9 Statistical Review (SR) Tables A.3, A.4, and A.5].

Table 1 - Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Daily Number of Moderate-to-Severe Hot Flushed during Therapy in All Subjects with an average minimum $\geq$ 8 Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF.

Week	1 90 µL E_2 Spray N = 76	1 Placebo Spray N =77	2 90 µL E_2 Sprays N = 74	2 Placebo Sprays N = 76	3 90 µL E_2 Sprays N = 76	3 Placebo Sprays N =75
Baseline						
Mean Number	11.81	12.41	12.66	12.13	10.78	12.55
Week 1						
Mean Number	8.34	10.12	8.25	9.36	7.99	9.52
Mean Change	-3.47	-2.29	-4.41	-2.77	-2.79	-3.03
p-value vs. placebo	0.0874		0.0364		0.2604	
Week 2						
Mean Number	7.06	9.40	6.73	8.12	5.99	8.65
Mean Change	-4.75	-3.01	-5.93	-4.01	-4.39	-3-90
p-value vs. placebo	0.0320		0.0218		0.0446	
Week 3						
Mean Number	6.26	9.08	6.08	7.69	5.19	7.90
Mean Change	-5.55	-3.33	-6.58	-4.44	-5.59	-4.65
p-value vs. placebo	0.0053		0.0087		0.0065	
Week 4						
Mean Number	5.55	8.77	5.36	7.39	4.14	8.01
Mean Change	-6.26	-3.64	-7.30	-4.74	-6.64	-4.54
p-value vs. placebo	0.0010		0.0027		0.0002	

Week	1 90 µL E_2 Spray N = 76	1 Placebo Spray N =77	2 90 µL E_2 Sprays N = 74	2 Placebo Sprays N = 76	3 90 µL E_2 Sprays N = 76	3 Placebo Sprays N =75
Week 5						
Mean Number	5.05	8.70	4.76	7.29	3.36	7.60
Mean Change	-6.76	-3.71	-7.90	-4.84	-7.32	-4.95
p-value vs. placebo	<0.0001		<0.0001		<0.0001	
Week 6						
Mean Number	4.69	8.37	4.38	6.82	3.06	7.58
Mean Change	-7.12	-4.04	-8.28	-5.31	-7.62	-4.97
p-value vs. placebo	0.0008		<0.0001		<0.0001	
Week 7						
Mean Number	4.39	8.15	4.26	6.90	2.70	7.38
Mean Change	-7.42	-4.26	-8.40	-5.23	-7.98	-5.17
p-value vs. placebo	0.0003		0.0007		<0.0001	
Week 8						
Mean Number	3.96	7.94	4.19	6.65	2.62	7.18
Mean Change	-7.85	-4.47	-8.47	-5.48	-8.06	-5.37
p-value vs. placebo	0.0001		0.0017		<0.0001	
Week 9						
Mean Number	3.96	8.11	4.03	6.20	2.38	7.16
Mean Change	-7.85	-4.30	-8.63	-5.93	-8.30	-5.39
p-value vs. placebo	<0.0001		0.0049		<0.0001	
Week 10						
Mean Number	3.79	8.19	4.11	6.22	2.20	7.13
Mean Change	-8.02	-4.22	-8.55	-5.91	-8.48	-5.42
p-value vs. placebo	0.0002		0.0067		<0.0001	
Week 11						
Mean Number	3.74	7.90	3.98	6.04	2.01	7.15
Mean Change	-8.07	-4.51	-8.68	-6.09	-8.67	-5.40
p-value vs. placebo	0.0003		0.0067		<0.0001	
Week 12						
Mean Number	3.71	7.65	4.00	5.94	2.24	7.23
Mean Change	-8.10	-4.76	-8.66	-6.19	-8.44	-5.32
p-value vs. placebo	0.0004		0.0099		<0.0001	

The results for each of the 1-, 2- and 3-90 µL estradiol transdermal spray treatment groups compared to the results for matching placebo treatment groups demonstrated both clinically and statistically significant (at the 0.05 significance level or less) reductions in frequency at Week 4 and Week 12 (the time points of assessment for the primary endpoint).

The primary efficacy analyses for severity of vasomotor symptoms are shown in Table 2 (adapted from MOR Tables 6, 8 10 and SR Tables A.3, A.4, and A.5).

Table 2 - Mean Severity of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Severity of Moderate-to-Severe Hot Flushed during Therapy in All Subjects with an average minimum ≥ 8 Moderate-to-Severe Hot Flushes Per Day at Baseline, Intent-to-Treat Population with LOCF.

Week	1 90 µL E_2 Spray N = 76	1 Placebo Spray N =77	2 90 µL E_2 Sprays N = 74	2 Placebo Sprays N = 76	3 90 µL E_2 Sprays N = 76	3 Placebo Sprays N =75
Baseline						
Mean Severity	2.53	2.55	2.54	2.54	2.58	2.54
Week 1						
Mean Severity	2.32	2.41	2.33	2.42	2.45	2.46
Mean Change	-0.21	-0.14	-0.21	-0.12	-0.13	-0.08
p-value vs. placebo	0.5301		0.4356		0.3019	
Week 2						
Mean Severity	2.26	2.38	2.16	2.31	2.37	2.44
Mean Change	-0.27	-0.17	-0.38	-0.23	-0.21	-0.10
p-value vs. placebo	0.4582		0.2683		0.0902	
Week 3						
Mean Severity	2.15	2.39	2.06	2.29	2.24	2.44
Mean Change	-0.38	-0.16	-0.48	-0.25	-0.34	-0.10
p-value vs. placebo	0.0997		0.0512		0.0058	
Week 4						
Mean Severity	2.06	2.36	1.97	2.29	2.15	2.41
Mean Change	-0.47	-0.19	-0.57	-0.25	-0.43	-0.13
p-value vs. placebo	0.0573		0.0160		0.0031	
Week 5						
Mean Severity	1.96	2.38	1.91	2.23	1.95	2.36
Mean Change	-0.57	-0.17	-0.63	-0.31	-0.63	-0.18
p-value vs. placebo	0.0034		0.0239		0.0004	
Week 6						
Mean Severity	1.85	2.33	1.85	2.15	1.73	2.35
Mean Change	-0.68	-0.22	-0.69	-0.39	-0.85	-0.19
p-value vs. placebo	0.0029		0.0398		<0.0001	
Week 7						
Mean Severity	1.79	2.33	1.79	2.16	1.67	2.34
Mean Change	-0.74	-0.22	-0.75	-0.38	-0.91	-0.20
p-value vs. placebo	0.0008		0.0241		<0.0001	

Week	1 90 µL E_2 Spray N = 76	1 Placebo Spray N =77	2 90 µL E_2 Sprays N = 74	2 Placebo Sprays N = 76	3 90 µL E_2 Sprays N = 76	3 Placebo Sprays N =75
Week 8						
Mean Severity	1.69	2.30	1.78	2.12	1.69	2.30
Mean Change	-0.84	-0.25	-0.76	-0.42	-0.89	-0.24
p-value vs. placebo	0.0008		0.0423		<0.0001	
Week 9						
Mean Severity	1.62	2.30	1.67	2.09	1.57	2.30
Mean Change	-0.91	-0.25	-0.87	-0.45	-1.01	-0.24
p-value vs. placebo	<0.0001		0.0124		<0.0001	
Week 10						
Mean Severity	1.61	2.30	1.66	2.06	1.62	2.28
Mean Change	-0.92	-0.25	-0.88	-0.48	-0.96	-0.26
p-value vs. placebo	<0.0001		<0.0001		<0.0001	
Week 11						
Mean Severity	1.55	2.30	1.67	2.07	1.47	2.28
Mean Change	-0.98	-0.25	-0.87	-0.47	-1.11	-0.26
p-value vs. placebo	<0.0001		0.0313		<0.0001	
Week 12						
Mean Severity	1.49	2.29	1.62	2.00	1.51	2.23
Mean Change	-1.04	-0.26	-0.92	-0.54	-1.07	-0.31
p-value vs. placebo	<0.0001		0.0406		<0.0001	

The results for the 2- and 3-90 µL estradiol transdermal spray treatment groups compared to the results for the matching placebo treatment groups demonstrated a statistically significant (at the 0.05 significance level or less) reduction in severity at Week 4 and Week 12 (the time points of assessment for the primary endpoint). The significance value for the results for the 1-90 µL estradiol transdermal spray treatment group compared to the result for the matching placebo treatment group was slightly above the 0.05 significance level at Week 4 (p=0.0573). However, I believe that a 0.0573 value can be accepted (and similar slightly elevated values in other previous unrelated applications have been accepted) as demonstrating efficacy for severity at this time point. This (acceptability) is further supported by the significance value of 0.0034 for severity at Week 5 and the highly significant treatment effect for frequency at Week 4 for the 1-90 µL estradiol transdermal spray treatment group (p=0.0010) when compared to the result for the matching placebo treatment group.

The Draft HT Clinical Trial Guidance recommends that clinical trials for drug products seeking to demonstrate efficacy for the treatment of moderate-to-severe vasomotor symptoms show both a statistically and clinically significant reduction from baseline vs. placebo in frequency and a statistically significant reduction from baseline vs. placebo in severity of hot flushes beginning at Week 4 and persisting through Week 12. A clinically significant reduction in frequency is defined as at least two more than placebo per day or

at least 14 more than placebo per week. The endpoints for efficacy for VMS (hot flushes) are:

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

Consistent with the Draft HT Clinical Trial Guidance recommendation, the 1-, 2- and 3-90 μL estradiol transdermal spray doses were all shown to be efficacious in the reduction of the frequency and severity of vasomotor symptoms at Week 4 and Week 12 of treatment. There was a lot of variability in the results with no clear dose responsiveness evident in the efficacy results.

The Sponsor also reported on a number of subgroup (secondary) analyses including: the frequency of hot flushes at Week 4 and Week 12 in subjects who were less than 50 years of age, subjects who were between the ages of 50-59 and subjects greater than 59 years of age and subjects who were surgically menopausal vs. naturally menopausal. Summation of these subgroup analyses show the following trends:

- There were 140 subjects who were < 50 years of age. At week 4 none of the subjects in the 3 spray group achieved the 0.05 significance level; at week 12, the 3-spray and the 1-spray achieved the p= 0.05 significance level.
- There were 259 subjects who ranged in age between of 50 and 59. At week 4 all three treatment groups had achieved the p = 0.05 significance level. At week 12, the 3-spray and the 1-spray doses maintained the p= 0.05significance level while the 2-spray dose showed a positive statistical trend of p = 0.0574 (Table 14.7.1.5).
- There were 57 subjects who age was > 59 years. At week 4 none of the treatment groups achieved a p =0.05 significance level; at week 12, the 3-spray and the 1-spray dosages maintained a p = 0.05 significance level (Table 14.7.1.6).
- The number of subjects who were surgically menopausal was 174. At week 4 the 2-spray dose achieved a p=0.05 significance level. At 12 weeks all three treatment group achieved a p = 0.05 significance level (Table 14.7.1.9).
- The number of subjects in the naturally menopausal group was 280. At weeks 4 and 12 the 3-spray and the 1-spray doses achieved the p 0.05 significance level. The 2-spray dose did not achieve statistical significance at either week 4 or 12.

EST-01 was not powered to demonstrate differences in the subgroup analyses. Nevertheless, in the age group for which treatment for hot flushes is most commonly sought, the 50-59 age group (the age group with the greatest number of subjects), the results are supportive of the primary analyses results.

Safety

Data from EST-01 combined with 3 Phase 2 studies (EST-02, EST-06 and FHRT-06) formed the Integrated Summary of Safety. The ISS summarizes data on a total of 454 subjects from EST-01, 71 subjects from Studies EST-02, 20 subjects EST-06 and 11 subjects from FHRT-06

In Study EST-01, approximately 458 subjects were randomized into treatment, 454 received at least one dose of test material and were analyzed for safety in the intent-to-treat population. The duration of exposure for the 3-spray estradiol dose was 85.7± 18.2 days and 74.1 ± 28.6 days for placebo; for the 2 spray estradiol dose, the duration of exposure was 78.3 ± 21.8 days and 79.0 ± 21.5 days for placebo; for the 1-spray estradiol dose, the duration of exposure was 83.1 ± 21.5days and 75.9 ± 27.2 days for placebo.

Endometrial hyperplasia

One of the most concerning adverse events most commonly associated with use of unopposed estrogens in women with a uterus is endometrial hyperplasia. Consistent with the Draft HT Clinical Trial Guidance recommendation for 12 week trials for VMS and VVA, in Study EST-01endometrial biopsies were obtained *at screening* and *at the end of treatment in subjects with an intact uterus* to evaluate possible proliferative effects. Subjects with an intact uterus were administered a daily dose of medroxyprogesterone acetate (MPA) 5 mg or 10 mg for 2 weeks *after* the end of treatment to oppose any estrogen-induced endometrial proliferation that might have occurred. Overall, 75 (33.2%) estradiol treatment subjects and 78 (34.2%) placebo subjects received MPA therapy. A follow-up visit was conducted at 4 ± 1 week after the end of treatment for subjects without an intact uterus or 4 ± 1 week after the end of MPA therapy for subjects who had an intact uterus.

Table 3 (modified from MOR Table 15) provides the endometrial histology results from end-of-study biopsies.

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Table 3: Endometrial Histology Results from Biopsies Obtained at End-of-Study EST-01(Week 12) or Early Exit (Visit 5). (ISS Safety Population)

	1 90 µL E_2 Spray N = 77	1 Placebo Spray N = 77	2 90 µL E_2 Spray N = 76	2 Placebo Spray N = 76	3 90 µL E_2 Spray N = 76	3 Placebo Spray N = 76
n	25	19	20	25	30	27
Histology						
0-no sample	1 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.7%)
1-insufficient	1 (4.0%)	3 (15.8%)	0 (0%)	2 (8%)	4 (13.3%)	6 (22.2)
2-Atrophic	14 (56.0%)	12 (63.2%)	8 (40.0%)	19 (76.0%)	7 (23.3%)	16 (59.3%)
3-Inactive	5 (20.0%)	1 (5.3%)	4 (20.0%)	1 (4.0%)	13 (43.3)	3 (11.1)
4-Proliferative	4 (16.0%)	3 (15.8%)	6 (30.0%)	3 (12.0%)	6 (20.0%)	1 (3.7%)
5-Secretory	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6-Menstrual	0 (0%)	0 (0%)	1 (5.0%)	0 (0%)	0 (0%)	0 (0%)
7-Simple Hyperplasia	0 (0%)	0 (0%)	1 (5.0%)	0 (0%)	0 (0%)	0 (0%)
8-Complex Hyperplasia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

The endometrial histology results, as assessed at the end-of-study or early exit visit, were not concerning. No cases of endometrial cancer or complex endometrial hyperplasia were demonstrated. A single case of endometrial hyperplasia was identified. Subject 6340101 (2-transdermal estradiol spray group) exhibited simple hyperplasia without atypia at the end of treatment that was reported as an adverse event (mild in severity; possibly related to treatment). As expected there was an increase in proliferation following estradiol treatment for all doses (baseline data is not shown in Table 3). Numerically, there was an increase in the percent proliferation between the 1- and 2-spray dosing, but not between 2- and 3-sprays (contrary to what might have been expected).

Other Serious Adverse Events

No deaths occurred during the conduct of primary, Phase 3 Study EST-01 or any of the Phase 2 studies.

EST-01

In Phase 3 Study EST-01, nine serious adverse events were reported in 8 subjects (7 transdermal estradiol spray treated subjects and 1 subject receiving placebo) who were randomized and who received study medication. The events included: dyspnea, exacerbation of COPD (2 subjects), uterine prolapse, spinal column stenosis, impaired gastric emptying, chest pain in the 7 subjects treated with transdermal estradiol spray and palpitations and dizziness in 1 placebo treated subject.

Twelve (12) subjects withdrew from the study (6 in the transdermal estradiol spray treatment groups and 6 in the placebo groups) for treatment emergent adverse events

(TEAs). In the transdermal estradiol spray groups, 5 subjects were withdrawn due to adverse events considered related to treatment (ovarian cyst, headache, nipple pain, chest pain and nausea). In the placebo groups, 3 subjects withdrew due to treatment-related events (increased blood pressure, pruritic rash, vaginal hemorrhage).

TEAEs of any severity were reported in 243 subjects (53.3% of the total subjects); 129 subjects treated with transdermal estradiol spray (57.1% of total subjects treated with the transdermal estradiol spray) and 114 placebo subjects (50% of the total placebo-treated subjects) reported adverse events

Headache was the most frequently reported common adverse event; with 24 (10.6%) transdermal estradiol spray treated subjects (8 in the 3-spray, 9 in the 2-spray and 7 in the in the 1-spray) reporting headache. Breast tenderness was reported in 13 (5.5%) transdermal estradiol treated subjects and 4 (1.8%) placebo treated subjects. Metrorrhagia was reported in 7 (3.1%) transdermal estradiol spray treated subjects and 2 (0.9%) placebo treated subjects. Nausea, back pain, nasopharyngitis and arthralgia were reported in 15 (3.3%), 12 (2.6%) and 10 (2.2%) subjects, respectively. No dose proportionality in the adverse events was evident.

EST-02

There were no serious adverse events or discontinuations due to an adverse event. There were 6 adverse events reported by 3 subjects. One subject, who received treatment with 1- estradiol transdermal spray, had 4 adverse events [paraesthesia and hypoesthesia in right lower extremities (Day6), paraesthesia to both hands (Day8) and rash to left side of the face (Day 6)]. A second subject had chest wall pain and a third subject had a toothache.

EST-06

There were no serious adverse events or discontinuations due to an adverse event. Four (4) adverse events were reported by 4 different subjects. Body ache was reported in three subjects and lower back pain was reported in 1 subject.

Study FHRT-06

There were no serious adverse events or discontinuations due to an adverse event.

DSI

No Division of Scientific Investigation (DSI) audit processes were sought under this NDA. There were no irregularities noted during review that resulted in a request for "for cause" inspection.

Clinical Pharmacology

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 Phase3 Study EST-01.

EST-02

Study EST-02 was a parallel study involving 72 subjects with 24 female subjects in each treatment group. The three treatment groups were 1 spray, 2-spray, and 3-spray groups. Plasma 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-prays, so were C_{max} values. For estrone and estrone sulfate, the increases in AUC and C_{max} from 1-spray to 2-sprays, though not dose proportional, were much higher than those from 2-sprays to 3-sprays. The T_{max} of estradiol from the three doses studied ranged 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 Sponsor pointed to the Day 1-Day 13 pre-dose 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.

EST-06

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 subject's 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 T_{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.

Study FHRT-06

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 $AUC_{(0-24)}$ and 86.6%-189% for C_{max}.

[redacted] b(4)

The Phase 3 Study EST-01 involved 428 subjects included in the efficacy evaluable analysis who were treated with three doses (1-spray, 2-spray, 3-spray) of transdermal estradiol spray 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. 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 Sponsor's June 15, 2007 amendment, the estradiol exposure (taken 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.

Pre-Clinical Pharmacology and Toxicology

In an advice letter dated January 20, 2006, DRUP indicated to the Sponsor, 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 Pharmacology/Toxicology reviewer recommendations for nonclinical studies. Excipients or impurities were not present at levels that pose a toxicological concern. There are no nonclinical safety issues relevant to clinical use. The Pharmacology/Toxicology reviewer has no recommendations for changes in the proposed labeling for Evamist™.

Based on the known pharmacology, pharmacokinetics and toxicology of transdermal and orally administered estradiol, the Pharmacology reviewer has recommended approval from a Pharmacology/Toxicology perspective.

Chemistry, Manufacturing and Controls (CMC):

The drug substance is Estradiol with a molecular formula of $C_{18}H_{24}O_2 \cdot 1/2H_2O$ and molecular weight of 281.4. The Sponsor cross referenced DMF — for CMC information on the drug substance, Estradiol. This DMF was previously reviewed and found to be adequate on January 27, 2006. No updated information was submitted to the DMF after the original review The Sponsor has provided adequate acceptance specifications and Certification of Analysis for the drug substance. The manufacturing facility received an "Acceptable" recommendation from the Office of Compliance. b(4)

The drug product is an estradiol transdermal spray. Each actuation delivers 90 µl of spray, containing 1.53 mg estradiol. The daily dose is 1-3 sprays/day. The drug product is a single-phase solution of estradiol (1.7% w/v) and a penetration enhancer (octisalate , in alcohol. The estradiol solution is filled into a glass vial with a neck finish. Each vial contains 8.1 ml of solution and is closed with a 90

µl. — spray pump topped with — Each container is designed to deliver 56 individual spray doses. The glass vial is encased in a — — applicator with a conical bell opening that controls the distance, angle, and area of the metered-dose spray. b(4)

The manufacturing process is

b(4)

The Sponsor provided sufficient information regarding the container/closure system in this NDA. Test results for extractable/leachable of the container/closure are reviewed and are acceptable, concurred by Pharmacology/Toxicology reviewer. The Sponsor reported that active residue was found to be built up on the nozzle and shroud, but the sponsor explained that the built up would not impact the spray pattern. Based on the consistent content uniformity results throughout the container lifetime, the Sponsor's justification is acceptable.

The Sponsor proposed a regulatory specification using PTIT (Parametric Tolerance Interval Testing) for the drug product. PTIT is a new statistical approach for the dose content uniformity testing, initiated for the pulmonary drug products. The review of this method is based on Agency's previous experience with the pulmonary products.

b(4)

The Sponsor provided 18 month long term stability data for 2 batches, 12 months long term stability data for one batch and 6 month accelerated stability data for all three batches of drug product. No change in the estradiol content and no degradation products of estradiol were detected.

b(4)

. No change in spray pattern was observed over time. There were a few failures of spray content uniformity at the end of container life. The Sponsor provided an acceptable justification for the failure. Over all, changes in the stability results are not significant. Based on the stability data, the Sponsor's proposal of 24 month expiration date is acceptable.

The Sponsor provided a comparability protocol for an — of the drug product container and proposed a CBE 30 supplement for the — The container components and metered applicator remain the same. Based on the current stability results, the proposed comparability protocol for the CBE 30 supplement of the — of the drug products is acceptable. b(4)

The manufacturing facility was inspected with an "Acceptable" recommendation from the Office of Compliance.

The Sponsor proposed to use "estradiol transdermal spray" as the established name, which is acceptable. Some minor modifications for the labeling were provided during the labeling review. From a CMC standpoint, all final labeling including the major Physician Insert and Patient Product Label, and Carton and Immediate Container Labels are acceptable.

From a CMC perspective the application can be approved.

Microbiology:

A Microbiology consult was provided at EOP2 by Dr. Langille on March 31, 2003. The consult was requested by the CMC reviewer because of the Sponsor's decision to provide specifications for microbial limit testing but not to test for the absence of objectionable organisms prior to release. Dr. Langille concluded "the odds of an objectionable organism surviving in a solution consisting of — ethanol are extremely low. This, along with the fact that Estradiol MDTS has a trans-dermal route of administration, results in a minimal public health risk due to the proposed change in microbial testing." b(4)

Product Name

On September 28, 2006, a consultation for evaluation of the trade name "Evamist™" was sent to the Division of Medication Errors and Technical Support (DMETS). DMETS provided the following comments on July 2, 2007.

DMETS has no objections to the use of the proprietary name, Evamist™. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

DDMAC finds the proposed proprietary name, Evamist™, acceptable from a promotional perspective.

Conclusions and Recommendations

Treatment with each of the 1-, 2- and 3-90 µL estradiol transdermal spray dose when compared to treatment with matching placebo was shown to have both a clinically and statistically significant reduction in the frequency of vasomotor symptoms at Week 4 and Week 12 and statistically significant reduction in severity of vasomotor symptoms at Week 4 and Week 12. Though treatment with each dose demonstrated efficacy, there was no clear dose responsiveness in treatment as would be expected with an estradiol product. In assessing mean frequency (number) change, the greatest difference between an estradiol transdermal spray treatment group and placebo treatment group at Week 4 and Week 12 was shown with the 1-spray dosage. For the mean change in severity of hot flushes, the greatest mean change difference between an estradiol transdermal spray dose and a placebo dose at Week 4 is that shown by the 2-spray dose, while at Week 12 the greatest mean change difference relative to placebo is demonstrated with the 1 spray dose. The lack of dose responsiveness seen in the symptom-relief data is consistent with the PK information as obtained by sparse sampling in the Phase 3 trial. 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. There was no dose response relationship based on the data on Day 14. The lack of dose responsiveness is not explained by information in the clinical trials. One can assume that this might result from a differential delivery or absorption with the three doses. There is no reason to suspect the latter. The review team examined the actual device and notes that the conical design of the spray device for skin delivery system has the potential for variability of delivery to the forearm of women with varying forearm surface areas. In women with small forearm surface area, part of the delivered spray is potentially wasted to the side of the arm without contact to actual surface area. This reviewer believes that this potential variability in product delivery (with actual loss of product external to this skin in some women) may account for the high degree of variability in the symptom relief data and the pharmacokinetic data and may account for the lack of true dose proportionality in the results. This problem would have most likely been avoided, if the Sponsor had chosen to study efficacy utilizing application at a body site with a greater skin surface area than the inner forearm. [redacted] b(4)

[redacted] However, application to the inner thigh was not bioequivalent to application to the forearm; the 90% CI was 83.2%-149% for AUC0-24 and 86.6%-189% for C_{max}. Given the lack of dose responsiveness and the high degree of variability demonstrated in both symptomatic efficacy results and the PK parameters, the Sponsor is strongly urged to study in Phase 4, effectiveness at this alternative site.

Despite the lack of demonstration of dose responsiveness in the efficacy results of the primary clinical trial, treatment with all three of the proposed dosages demonstrated efficacious results. No safety concerns were demonstrated with any dose. It is this reviewer's belief that even in the absence of demonstration of dose responsiveness in the clinical trial, in actual market use, some individual women may receive benefit from the 3- spray dose beyond that of the 2-sprays dose. The Division has long considered that multiple doses of estrogen products, meeting the criteria for safety as well as efficacy, should be available to titrate the dose in individual patients who do not get acceptable

relief from the lower doses. Therefore, I concur with the Primary Clinical and Statistical reviewers and recommend that all three efficacious and safe transdermal estradiol spray doses (1-spray, 2-spray and 3-spray) be approved and be available to titrate the dosage of estradiol, if necessary for the individual patient.

Comments from the Division of Surveillance, Research and Communications and Division of Medication Errors and Technical Support were received on February 12, 2007 and July 2, 2007, respectively. These comments were all reviewed and incorporated, where appropriate, into Medical Officer labeling review. Comments from the SEAL were received on July2, 2007 and were incorporated into the label.

Labeling negotiations have been completed and the final negotiated acceptable label is to be made part of the final decisional package.

Shelley R. Slaughter, M.D., PhD
Medical Officer Team Leader and
Group Leader for NDA 22-014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shelley Slaughter
7/27/2007 12:39:29 PM
MEDICAL OFFICER

Scott Monroe
7/27/2007 01:20:52 PM
MEDICAL OFFICER
I concur with Dr. Slaughter's conclusions and her recommendation for approval of Evamist (estradiol transdermal spray) for the treatment of moderate to severe vasomotor symptoms due to menopause.