CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-014

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Specification for Spray Content Uniformity for EvaMist® (Estradiol Transdermal Spray)

NDA/SERIAL NO.:	NDA 22014
DRUG NAME:	EvaMist® (Estradiol Transdermal Spray)
SPONSOR:	VIVUS, INC
DATE RECEIVED BY CENTER:	September 28, 2006
REVIEW PRIORITY:	Standard
DOCUMENTS REVIEWED:	July 25, 2007
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Keywords: Spray content uniformity, PTIT.

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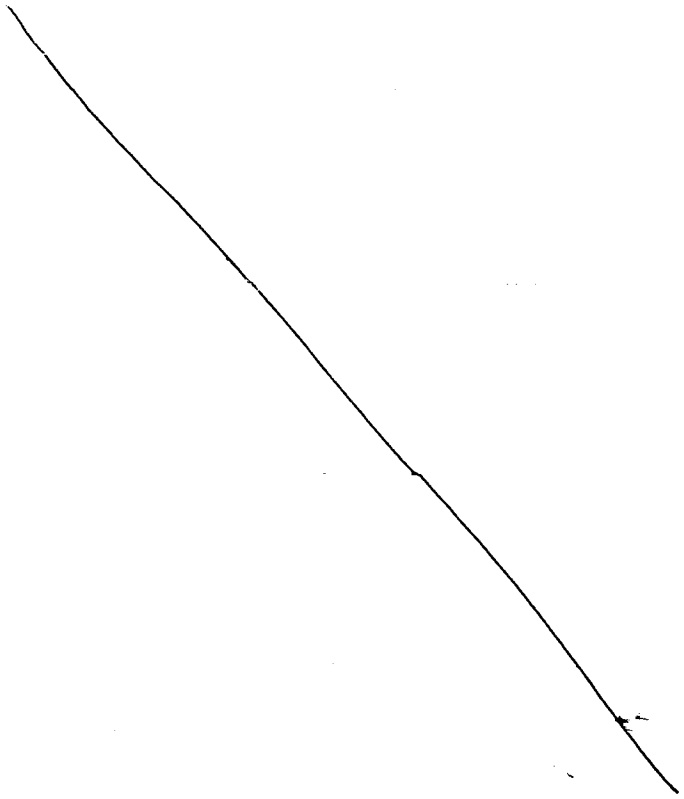
1. EXECUTIVE SUMMARY

This review describes statistical findings about sponsor's proposed specification for spray content uniformity in response to the consult request of FDA Office of New Drug Quality Assessment.

VIVUS, INC proposed the Parametric Tolerance Interval Test (PTIT) to establish acceptance criteria for spray content uniformity at the beginning and end of container life for the estradiol transdermal spray product.



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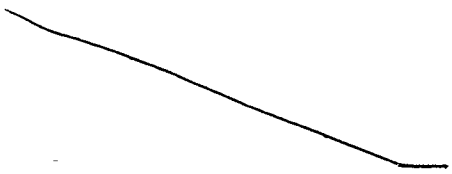

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Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number:	22-014 / 000
Drug Name:	Estradiol 1.7% transdermal spray (EvaMist)
Indication(s):	Treatment of moderate to severe vasomotor symptoms associated with menopause
Applicant:	VIVUS, Inc.
Date(s):	Letter Date: September 28, 2006 PDUFA Date: July 28, 2007
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
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Key Words: Clinical studies, NDA review, Multiple comparisons

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The one submitted study provides evidence demonstrating the efficacy of the 1-spray, 2-spray, and 3-spray doses of EvaMist (estradiol 1.7% transdermal spray), in terms of treatment of moderate to severe vasomotor symptoms associated with menopause, in postmenopausal women.

1.2 Background

The Sponsor has submitted one randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of EvaMist (estradiol 1.7% transdermal spray) in the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

The Sponsor's proposed indication is:

> *EvaMist is indicated for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.*

1.3 Statistical Issues and Findings

The one statistical issue in this submission is that the 1-spray dose does not achieve statistical significance for all four co-primary endpoints, in particular, severity of moderate and severe hot flushes at week 4 (p=0.0573). To address this issue, a by-week presentation of efficacy is presented to observe the trend in reduction of severity. Interpretation of this by-week presentation is done by the clinical reviewer to determine if there is a clinically meaningful trend in reduction of severity after Week 4. The clinical reviewer has determined that the trend is clinically meaningful and provides evidence of efficacy for reduction in severity of moderate to severe hot flushes after Week 4 for the 1-spray dose.

These study results provide evidence of efficacy for the 1-spray, 2-spray, and 3-spray doses of EvaMist, in terms of treatment of moderate to severe vasomotor symptoms associated with menopause, in postmenopausal women.

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted one clinical study (EST-01) designed to demonstrate the safety and efficacy of EvaMist (estradiol) for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause in postmenopausal women with an estimated average minimum of 8 moderate to severe hot flushes per day. Table 2.1 presents a brief summary of the study addressed in this review.

Table 2.1
Brief Summary of Clinical Study for EvaMist

Study Number (No. of Sites / Country) Study Conduct Dates	Subject Population	Treatment	Number Randomized (ITT[1])	Design[2]
EST-01 (43 / United States) Dec. 2004 to Mar. 2006	Postmenopausal women, 35 years or older, with or without uterus, with an average minimum of 8 moderate to severe hot flushes per day or mean total frequency of ≥56 per week during baseline evaluation period, and a BMI ≤35 kg/m^2.	Estradiol 1-spray Estradiol 2-spray Estradiol 3-spray Placebo 1-spray Placebo 2-spray Placebo 3-spray **Total**	77 (76) 76 (74) 76 (76) 77 (77) 76 (76) 76 (75) **458 (454)**	R, DB, PC, MC, PG

Source: Statistical Reviewer's listing.
[1] ITT = Intent to Treat (took at least one dose of study treatment)
[2] DB = Double-blind, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

The one statistical issue in this submission is that the 1-spray dose does not achieve statistical significance for all four co-primary endpoints, in particular, severity of moderate and severe hot flushes at week 4. My review presents the Applicant's primary efficacy analyses, with more detail to the by-week results for severity for all dose groups.

2.2 Data Sources

The study reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\N22014\N_000 under submission dates 9-28-06 and 10-13-06.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

In this study, eligible subjects were equally randomized to one of three estradiol 1.7% groups (*one 90 µL spray of estradiol, two 90 µL sprays of estradiol, three 90 µL sprays of estradiol*) or one of three matching placebo groups (*one 90 µL spray of placebo, two 90 µL sprays of placebo, or three 90 µL sprays of placebo*). Each spray is applied to adjacent non-overlapping areas on one inner forearm daily for 12 weeks. Subjects recorded daily the number and severity of hot flushes on a diary card for each 24-hour period for at least 7 consecutive days at baseline and for 12 weeks of treatment. The severity of hot flushes is defined as:

Mild = sensation of heat without sweating
Moderate = sensation of heat with sweating but able to continue activity
Severe = sensation of heat with sweating, causing you to discontinue activity

The primary efficacy objective is to assess the three estradiol doses compared to placebo for relief of moderate to severe vasomotor symptoms associated with menopause based on the weekly number and severity of hot flushes.

The four co-primary efficacy endpoints are the mean change from baseline (1) in the frequency of moderate to severe vasomotor symptoms at weeks 4 and 12 compared to placebo and (2) in the severity of moderate to severe vasomotor symptoms at weeks 4 and 12 compared to placebo. The average daily number of hot flushes and average daily severity score is calculated for each subject for the baseline week and for each of the 12 weeks of therapy.

The average number of moderate and severe hot flushes for each time period is calculated as:

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

The average severity of moderate to severe hot flushes for each time period is 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 is defined as all subjects randomized to treatment who receive at least one dose of study medication.

Missing daily frequency values are 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 is used (see Appendix for details). For subjects terminating the study prematurely, the LOCF method is used to provide data for scheduled assessments that were missed. Missing severity values are calculated from the imputed frequency values.

The primary analysis uses 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. Centers are pooled on the basis of geography (N, S, E, W) and testing is done using a t-test based on the ANCOVA model.

The three pairwise comparisons of each estradiol dose to its matching placebo are 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 is used where the 3-spray arms are compared first, then the 2-spray arms, followed by the 1-spray arms. Testing is stopped once a statistical test fails to reach significance for any of the 4 co-primary endpoints.

3.1.1 Overall Descriptive Statistics for Study EST-01

The following section presents demographic and baseline characteristics, and subject disposition for study EST-01.

For the ITT population, demographic and baseline characteristics are comparable among the treatment groups. The subjects' mean age ranges from 52.2 to 53.5 years for all estradiol doses and from 52 to 52.8 years for placebo. The majority of subjects are Caucasian (64.5% to 76.3%). The baseline values for the primary endpoints of number and severity of hot flushes are similar across treatment groups (Appendix Tables A.1 and A.2).

Table 3.3 presents the number of randomized subjects and the disposition of the subjects. Study discontinuation during for each treatment group: ranges from 9.4% to 17.2% in the estradiol groups, and ranges from 15.8% to 24.7% in the placebo groups. The primary reason for study discontinuation in the estradiol 1- and 3-spray treatment groups and placebo group is subject request and in the estradiol 2-spray group is lost to follow-up.

Table 3.3
Summary of Subject Disposition for Study EST-01

	Estradiol 1-spray	Placebo 1-spray	Estradiol 2-spray	Placebo 2-spray	Estradiol 3-spray	Placebo 3-spray
Randomized	77	77	76	76	76	76
Randomized and Used Test Article (ITT)*	76 (98.7)	77 (100.0)	74 (97.4)	76 (100.0)	76 (100.0)	75 (98.7)
Completed Study*	68 (88.3)	58 (75.3)	61 (80.2)	64 (84.2)	69 (90.8)	57 (75.0)
Discontinuations** n (%)	8 (10.5)	19 (24.7)	13 (17.6)	12 (15.8)	7 (9.2)	18 (24.0)
Discontinued Due to:						
Adverse Event[1] n (%)	*2 (25.0)*	*2 (10.5)*	*2 (15.4)*	*3 (25.0)*	*2 (28.6)*	*1 (5.6)*
Hurricane[2]	*1 (12.5)*	*3 (15.8)*	*3 (23.1)*	*2 (16.7)*	*0*	*4 (22.2)*
Lost to Follow-up	*1 (12.5)*	*1 (5.3)*	*4 (30.8)*	*1 (8.3)*	*2 (28.6)*	*4 (22.2)*
Compliance	*1 (12.5)*	*3 (15.8)*	*1 (7.7)*	*0*	*0*	*0*
Subject Request	*3 (37.5)*	*9 (47.4)*	*2 (15.4)*	*4 (33.3)*	*2 (28.6)*	*7 (38.9)*
Other	*0*	*1 (5.3)*	*1 (7.7)*	*2 (16.7)*	*1 (14.3)*	*2 (11.1)*

Source:Figure 2 on page 54, disposition description on page 55, and Table 7 on page 63 of Study EST-01 report.
* With respect to number of randomized subjects.
** With respect to number of ITT subjects.
[1] With respect to number of discontinuations
[2] Subject discontinued due to Hurricane Katrina event

3.1.2 Study EST-01 Results: Number and Severity of Moderate and Severe Hot Flushes at Week 4 and Week 12

The Applicant's results for the four co-primary efficacy endpoints of number of moderate and severe hot flushes and severity of moderate and severe hot flushes at Week 4 and Week 12 are presented in Table 3.4 below and in greater detail in the Appendix in Tables A.1 through A.5. I concur with the Applicant's results.

Efficacy results for frequency and severity of moderate to severe hot flushes based on the co-primary efficacy endpoints are presented in Table 3.4 and are described below:

- Both the 2- and 3-spray estradiol doses demonstrate a reduction in the frequency and severity of moderate to severe hot flushes compared to placebo at Weeks 4 and 12 ($p<0.05$ for all four co-primary endpoints).
- The 1-spray estradiol dose demonstrates a reduction in the frequency of moderate to severe hot flushes compared to placebo at Weeks 4 and 12 ($p<0.01$) and a reduction in the severity of moderate to severe hot flushes compared to placebo at Week 12 only ($p<0.0001$).

The 1-spray dose does not demonstrate a reduction in the severity of moderate to severe hot flushes compared to placebo at Week 4 ($p=0.0573$). To address this issue, the clinical reviewer requested that severity score be presented by week to observe if there is a trend in reduction of severity after Week 4 (see Table A.5 in Appendix). After Week 4, the change from baseline for the estradiol 1-spray group's values consistently decrease over time, whereas the placebo group's values level off at about -0.25 from Week 5 onwards. The clinical reviewer has determined that the trend in reduction of severity for all weeks after week 4 is clinically meaningful and provides evidence of efficacy for reduction in severity of moderate to severe hot flushes starting at week 5 for the estradiol 1-spray dose.

Table 3.4
Study EST-01: Changes in Frequency (Number) and Severity of Moderate to Severe Hot Flushes at Weeks 4 and 12 (ITT Population)

	Adjusted* Mean Change from Placebo (p-value)		
	Estradiol 1 spray	Estradiol 2 spray	Estradiol 3 spray
$n_{Estradiol}$ / $n_{Placebo}$	76 / 77	74 / 76	76 / 75
Week 4			
Number of moderate and severe hot flushes	-2.5 (0.0010)	-2.4 (0.0027)	-3.3 (0.0002)
Severity of moderate and severe hot flushes	-0.2 (0.0573)	-0.3 (0.0160)	-0.3 (0.0031)
Week 12			
Number of moderate and severe hot flushes	-3.0 (0.0004)	-2.1 (0.0099)	-4.0 (<0.0001)
Severity of moderate and severe hot flushes	-0.7 (<0.0001)	-0.3 (0.0406)	-0.7 (<0.0001)

Source: Tables 14.7.1.1 and 14.7.2.1 in Section 14, Vol.29, pages 202 of 269 and 236 of 269 of Study EST-01 report.
* Based on ANCOVA model with treatment, region, and treatment-by-region interaction as factors and baseline severity score as covariate.

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

There are no subgroup populations of interest in this submission.

5. CONCLUSIONS

Based on the number and severity of hot flushes at Week 4 and Week 12 and by-week values, the results of study EST-01 provide evidence of efficacy for the 1-spray, 2-spray, and 3-spray doses of EvaMist (estradiol), in terms of treatment of moderate to severe vasomotor symptoms associated with menopause, in postmenopausal women.

APPENDIX

1. Tables

Table A.1
Study EST-01: Frequency of Moderate to Severe Hot Flushes at Week 4 and Week 12 (ITT Population)

	Estradiol 1 spray	Placebo 1 spray	Estradiol 2 sprays	Placebo 2 sprays	Estradiol 3 sprays	Placebo 3 sprays
n	76	77	74	76	76	75
Baseline mean	11.8	12.4	12.7	12.1	10.8	12.6
Week 4 Adjusted* Mean Values						
Change from baseline	-6.2	-3.7	-7.5	-5.1	-7.1	-3.8
Treatment vs. Placebo Change (95% CI)	-2.5 (-3.9, -1.0)		-2.4 (-4.0, -0.9)		-3.3 (-5.0, -1.6)	
p-value for Treatment Difference	0.0010*		0.0027*		0.0002*	
Week 12 Adjusted* Mean Values						
Change from baseline	-8.1	-5.1	-8.6	-6.5	-8.8	-4.8
Treatment vs. Placebo Change (95% CI)	-3.0 (-4.6, -1.4)		-2.1 (-3.7, -0.5)		-4.0 (-5.3, -2.6)	
p-value for Treatment Difference	0.0004*		0.0099*		<0.0001*	

Source: Tables 14.7.1.1 and 14.7.2.1 in Section 14, Vol.29, page 202 of 269 of Study EST-01 report.
* Adjusted results based on ANCOVA model with treatment, region, and treatment-by-region interaction as factors and baseline severity score as covariate.
* Statistically significant after applying the step-down procedure described in the sentence above.

Table A.2
Study EST-01: Severity* of Moderate to Severe Hot Flushes at Week 4 and Week 12 (ITT Population)

	Estradiol 1 spray	Placebo 1 spray	Estradiol 2 sprays	Placebo 2 sprays	Estradiol 3 sprays	Placebo 3 sprays
n	76	77	74	76	76	75
Baseline mean	2.5	2.6	2.5	2.5	2.6	2.5
Week 4 Adjusted* Mean Values						
Change from baseline	-0.5	-0.2	-0.6	-0.3	-0.5	-0.1
Treatment vs. Placebo Change (95% CI)	-0.2 (-0.5, 0.0)		-0.3 (-0.6, -0.1)		-0.3 (-0.5, -0.1)	
p-value for Treatment Difference	0.0573		0.0160*		0.0031*	
Week 12 Adjusted* Mean Values						
Change from baseline	-1.0	-0.3	-0.9	-0.6	-1.1	-0.3
Treatment vs. Placebo Change (95% CI)	-0.7 (-1.0, -0.4)		-0.3 (-0.7, -0.0)		-0.7 (-1.1, -0.4)	
p-value for Treatment Difference	<0.0001*		0.0406*		<0.0001*	

Source: Tables 14.7.1.1 and 14.7.2.1 in Section 14, Vol.29, page 236 of 269 of Study EST-01 report.
* Adjusted results based on ANCOVA model with treatment, region, and treatment-by-region interaction as factors and baseline severity score as covariate.
* Statistically significant after applying the step-down procedure described in the sentence above.
Severity = (number moderate x 2) + (number severe x 3)/(number moderate + number severe)

Table A.3
Study EST-01: Frequency and Severity of Moderate to Severe Vasomotor Symptoms by Week (1-Spray Group)

	Frequency Moderate to Severe Vasomotor Symptoms (number/day)			Severity Score of Moderate to Severe Vasomotor Symptoms		
	Change from Baseline[1]			Change from Baseline[1]		
Week	Estradiol (n=76)	Placebo (n=77)	p-value[2]	Estradiol (n=76)	Placebo (n=77)	p-value[2]
1	-3.47	-2.29	0.0874	-0.21	-0.14	0.5301
2	-4.75	-3.01	0.0320	-0.27	-0.17	0.4582
3	-5.55	-3.33	0.0053	-0.38	-0.16	0.0997
4	-6.26	-3.64	0.0010	-0.47	-0.19	0.0573
5	-6.76	-3.71	0.0002	-0.57	-0.17	0.0034
6	-7.12	-4.04	0.0008	-0.68	-0.22	0.0029
7	-7.42	-4.26	0.0003	-0.74	-0.22	0.0008
8	-7.85	-4.47	0.0001	-0.84	-0.25	0.0006
9	-7.85	-4.30	<0.0001	-0.91	-0.25	<0.0001
10	-8.02	-4.22	0.0002	-0.92	-0.25	<0.0001
11	-8.07	-4.51	0.0003	-0.98	-0.25	<0.0001
12	-8.10	-4.76	0.0004	-1.04	-0.26	<0.0001

Source: Table 14.9.1.3, Vol.30, page 11 of 280 of Study EST-01 report.
[1] Change based on raw data.
[2] p-value based on ANCOVA model with treatment, region, and treatment-by-region interaction as factors and baseline value as covariate.

Table A.4
Study EST-01: Frequency and Severity of Moderate to Severe Vasomotor Symptoms by Week (2-Spray Group)

	Frequency Moderate to Severe Vasomotor Symptoms (number/day)			Severity Score of Moderate to Severe Vasomotor Symptoms		
	Change from Baseline[1]			Change from Baseline[1]		
Week	Estradiol (n=74)	Placebo (n=76)	p-value[2]	Estradiol (n=74)	Placebo (n=76)	p-value[2]
1	-4.41	-2.77	0.0364	-0.21	-0.12	0.4356
2	-5.93	-4.01	0.0218	-0.38	-0.23	0.2683
3	-6.58	-4.44	0.0087	-0.48	-0.25	0.0512
4	-7.30	-4.74	0.0027	-0.57	-0.25	0.0160
5	-7.90	-4.84	0.0004	-0.63	-0.31	0.0239
6	-8.28	-5.31	0.0009	-0.69	-0.39	0.0398
7	-8.40	-5.23	0.0007	-0.75	-0.38	0.0241
8	-8.47	-5.48	0.0017	-0.76	-0.42	0.0423
9	-8.63	-5.93	0.0049	-0.87	-0.45	0.0124
10	-8.55	-5.91	0.0067	-0.88	-0.48	0.0291
11	-8.68	-6.09	0.0067	-0.87	-0.47	0.0313
12	-8.66	-6.19	0.0099	-0.92	-0.54	0.0406

Source: Table 14.9.1.2, Vol.30, page 10 of 280 of Study EST-01 report.
[1] Change based on raw data.
[2] p-value based on ANCOVA model with treatment, region, and treatment-by-region interaction as factors and baseline value as covariate.

Table A.5
Study EST-01: Frequency and Severity of Moderate to Severe Vasomotor Symptoms by Week (3-Spray Group)

	Frequency Moderate to Severe Vasomotor Symptoms (number/day)			Severity Score of Moderate to Severe Vasomotor Symptoms		
	Change from Baseline[1]			Change from Baseline[1]		
Week	Estradiol (n=76)	Placebo (n=75)	p-value[2]	Estradiol (n=76)	Placebo (n=75)	p-value[2]
1	-2.79	-3.03	0.2604	-0.13	-0.08	0.3019
2	-4.39	-3.90	0.0446	-0.21	-0.10	0.0902
3	-5.59	-4.65	0.0065	-0.34	-0.10	0.0058
4	-6.64	-4.54	0.0002	-0.43	-0.13	0.0031
5	-7.32	-4.95	<0.0001	-0.63	-0.18	0.0004
6	-7.62	-4.97	<0.0001	-0.85	-0.19	<0.0001
7	-7.98	-5.17	<0.0001	-0.91	-0.20	<0.0001
8	-8.06	-5.37	<0.0001	-0.89	-0.24	<0.0001
9	-8.30	-5.39	<0.0001	-1.01	-0.24	<0.0001
10	-8.48	-5.42	<0.0001	-0.96	-0.26	<0.0001
11	-8.67	-5.40	<0.0001	-1.11	-0.26	<0.0001
12	-8.44	-5.32	<0.0001	-1.07	-0.31	<0.0001

Source: Table 14.9.1.1, Vol.30, page 9 of 280 of Study EST-01 report.
[1] Change based on raw data.
[2] p-value based on ANCOVA model with treatment, region, and treatment-by-region interaction as factors and baseline value as covariate.

2. Last Observation Carried Forward Procedure for Missing Data

When there are three or more days with missing data for a particular week, the LOCF is obtained in the following manner. If the 3 days before and 3 days after the day with a missing value does not have a total of 4 or more non-missing days, the average of the 7 previous days is assigned to the missing day (assuming those 7 days contain at least 4 non-missing days). If the 7 previous days to the missing day does not contain 4 or more non-missing days, the missing day is assigned the average value of the 4 previous non-missing days. If less than 4 previous non-missing days are available, the missing day is assigned the average value of the previous non-missing days. If a subject has no diary data available after the first dose of study drug administration, the baseline score is carried forward for all post baseline evaluations for that subject.

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