CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-367

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-367/S-000
Name of drug:	[redacted] (estradiol acetate vaginal ring)
Applicant:	Galen Limited
Indication:	• Treatment of moderate to severe vasomotor symptoms associated with menopause • [redacted]
Route of Administration	Vaginal
Strengths	0.05 mg /day and 0.10 mg /day
Documents reviewed:	Vol 1.1, 1.1.0, 1.142, 1.156
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Keywords:	NDA review, clinical studies

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS

Subjects treated with estradiol 0.05 mg/day and 0.10 mg/day experienced statistically significant improvement in the number of moderate-to-severe vasomotor symptoms (MSVS) and in the mean severity for MSVS as compared to placebo-treated subjects. A significant improvement in each active treatment group was detected at week 4, and maintained through weeks 8 and 12.

Subjects treated with estradiol 0.05 mg/day and 0.10 mg/day showed statistically significant increase in the percentage of superficial cells ($p< 0.001$). However, only subjects treated with estradiol 0.05 mg/day showed a statistically significant reduction in the percentage of parabasal cells. Note that increases in the superficial and intermediate cells and decreases in the parabasal cells are beneficial effects. For vaginal pH, only subjects treated with estradiol 0.05 mg/day showed a statistically significant improvement.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

In this NDA, the sponsor presented two clinical trials (Study IVR 1002 and Study HRT 008) to demonstrate the safety and efficacy of Estradiol acetate vaginal ring in the treatments of moderate-to-severe vasomotor symptoms (MSVS) and vulvar and vaginal atrophy (VVA) associated with the menopause. This reviewer focuses on study IVR 1002. Study HRT 008 does not comply with the Division's recommendations for inclusion criteria and it is supportive for safety only.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Hormone Therapy (HT) has been developed and shown to be effective for relief of MSVS and VVA. These include oral tablets and transdermal products. The Intravaginal delivery system developed by the sponsor is intended to allow a controlled release of estradiol-3-acetate for 12 weeks. The doses used in this study are equivalent to 0.05 mg and 0.10 mg of estradiol per day. The primary objectives of this study are to evaluate the efficacy and safety of IVRs releasing two doses of estradiol-3-acetate versus placebo for the treatment of MSVS and VVA.

2.2 DATA ANALYZED AND SOURCES

The SAS data sets and descriptions were provided by the sponsor to the EDR on April 4, 2001. Additional analyses of mean change from baseline to final evaluation for vaginal pH and maturation index from all treated subjects were requested on September 12 and received on September 15, 2002.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

Study IVR 1002 was a placebo-controlled, multicenter, double-blind, parallel group study in which healthy postmenopausal women were randomized to receive either IVRs releasing estradiol-3-acetate equivalent to 0.05 mg/day, or 0.10 mg/day, or placebo for 13 weeks. Table 1, below, summarizes the study.

Table 1
Summary of Controlled Trial

Report # (Protocol #)	Study Design	Treatment Group	Sample Size	Duration of treatment
RR 01101 (IVR 1002)	Double-blind, randomized, placebo-controlled, parallel group, multicenter study in postmenopausal women	Estradiol acetate IVR delivering at a rate equivalent to :	333	13 weeks
35 sites in US		0.05 mg /day	113	
10/25/99		0.10 mg/day	112	
4/18/01		Placebo IVR	108	

In this study, 333 subjects were randomized in 35 clinical sites in US; 108 to placebo, 113 to estradiol 0.05 mg/day, and 112 to estradiol 0.10 mg/day. A total of 54 (16.2%) of 333 subjects discontinued from the study. The sponsor noted that there were significantly more subjects in the placebo group who discontinued study treatment prematurely than in the estradiol 0.05 mg/day (p=0.007), and estradiol 0.10 mg/day (p=0.001). The sponsor used a one-way analysis of variance (ANOVA), with treatment group as the factor. Table 2 presents a summary of subject enrollment, randomization, and disposition.

Table 2
Subject disposition by Treatment

	Placebo	Estradiol 0. 05 mg/day	Estradiol 0.10mg/ day
Number of subjects randomized	108	113	112
Number (%) of subjects who completed study	79 (73.1%)	99 (87.6%)	101 (90.2%)
Number (%) of subjects in ITT efficacy population	105(97.2%)	111 (98.2%)	109 (97.3%)
Number (%) of subjects who did not complete study	29 (26.9%)	14 (12.4%)	11 (9.8%)
Reason for not completing:			
Adverse events	9 (8.3)	6 (5.3)	4 (3.6)
Withdrew consent	4 (3.7)	2 (1.8)	0 (0.0)
Protocol violation	3 (2.8)	1 (0.9)	3 (2.7)
Noncompliance	0 (0.0)	0 (0.0)	0 (0.0)
Insufficient study product	1 (0.9)	0 (0.0)	1 (0.9)
Lost of follow-up	0 (0.0)	1 (0.9)	1 (0.9)
Other	12 (11.1)	4 (3.5)	2 (1.8)

Source: Text-Tables T-2, T-3, T-6 of Vol. 108
All percentages are relative to the number of subjects randomized.

Out of 333 subjects, eight subjects were excluded from the study, there are 325 in the Intent-to-Treat (ITT) population:

- 6 discontinued on the 1st day of treatment:

2 - inability to retain the ring
2 - intolerance to the ring
2 - had adverse events

- 2 lost follow-up prior to having a post-baseline MSVS evaluation

Of the 325 ITT subjects, the majority (77.2%) of subjects are Caucasian with a mean age of 51.7 years. There were no statistically significant differences among treatment groups in age, weight, height, race, or smoking. The majority of subjects were nonsmokers (81.1%) and nondrinkers (87.7%). However, there was a significant difference among the 3 treatment groups in baseline alcohol consumption (p=0.007). This was due to the lower number of nondrinkers in the estradiol 0.1 mg/day group (79.5%) compared to the placebo group (91.7%) and in the estradiol 0.05 mg/day group (92%).

Treatment of MSVS

During the two weeks prior to randomization, subjects recorded the frequency and severity of hot flushes on a daily diary card. Subjects who experienced at least 7 MSVS per day or an average of 56 MSVS per week were eligible to be randomized to receive either estradiol 0.05 mg/day, or estradiol 0.10 mg/day, or placebo group.

The primary efficacy endpoints are the mean change from baseline in the number of MSVS and in the mean change in severity at weeks 4 and 12 using last observation carried forward (LOCF) from the intent-to-treat (ITT) population. Secondary efficacy endpoints are the mean percent changes from baseline in the number of MSVS at weeks 4, 8, and 12. MSVS score assigned were 0=no flushes, 1=mild, 2=moderate, and 3=severe. The percentage reduction was defined as follows: Percentage Reduction = [(Baseline – On treatment value)/Baseline]*100

The estimated sample size of 100 subjects per treatment arm (drop out rate assumed to be 15% in the first 4 weeks) in order to complete 85 available subjects was calculated using the 2-sample t-test. Per the sponsor, 85 subjects per group were be sufficient to detect a difference of 13 MSVS per week between active treatment groups to placebo in change from baseline with a power of 0.80 and a size of test α=0.05.

The sponsor used 2-way ANOVA with treatment and study center as factor effects to compare 0.05 mg/day and 0.10 mg/day of estradiol to placebo in MSVS analyses. The variables center effect and the treatment-by-center interaction were not statistically significant, therefore the final model considered only treatment effect. Table 3 summarizes the sponsor's MSVS analyses. The 95% confidence intervals (CI) were adjusted for multiple pairwise comparisons using Dunnett's method. A CI that excludes zero indicates that the treatment group is significantly difference from placebo at the α =0.05 level.

All MSVS efficacy analyses are based on an ITT population, with LOCF. The ITT is defined as all subjects randomized who inserted at least 1 IVR, had a baseline measurement of MSVS and had at least 1 MSVS evaluation following initiation of double-blind treatment. The LOCF approach was used to estimate missing data with the most recent non-missing evaluation.

Treatment of urogenital symptoms

To investigate the effects on atrophy, subjects with signs and symptoms of atrophy at baseline were summarized using 3 different measures. The 3 measures of atrophy were the subject assessment of vaginal symptoms, the maturation index, and the vaginal exam. This reviewer addresses only the maturation index.

Maturation Index

The maturation index was performed at baseline and at final evaluation. The maturation index was determined by establishing the percentage of 3 cell types present in the vagina: the 3 cell types were parabasal, intermediate, and superficial. Maturation Index was calculated from the percentages of each cell type using the following formula:

Maturation Index Score = (%Parabasal cell x 0.2) + (%Intermediate cells x 0.6) + (%Superficial cell x 1.0)

To determine treatment effect on vaginal atrophy, the maturation index was evaluated at baseline and at final evaluation using 2-way ANOVA with factors for treatment and study center. Subjects were considered having atrophy at baseline if their maturation index at baseline was ≤ 52. An increase in maturation index was considered an improvement.

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Treatment of MSVS

Table 3 presents the results of the sponsor's MSVS for ITT population using LOCF. The placebo group had a higher mean number of MSVS at baseline (83.1) compared to the estradiol 0.05 mg/day (73.8) and 0.10 mg/day (75.1). The sponsor's results show that the mean changes from baseline in the number of MSVS at weeks 4 and 12 were statistically significant greater as compared to the placebo group ($p<0.05$). The mean change from baseline in the severity of MSVS was significantly greater in the active treatment groups as compared to placebo at weeks 4 and 12 ($p<0.05$). Therefore, the sponsor concluded that the Estradiol Acetate is efficacious in the treatment of MSVS.

Table 3
Summary of Sponsor's MSVS Analyses (ITT and LOCF)

		Placebo N=105		Estradiol 0.05 mg/day N=111		Estradiol 0.1 mg/day N=109	
	Study Week	Mean	Mean change from baseline to subsequent week	Mean	Mean change from baseline to subsequent week (95% CI vs. Placebo)	Mean	Mean change from baseline to subsequent week (95% CI vs. Placebo)
Mean change from baseline in the number of MSVS	-2	83.6		73.8		75.1	
	4	51.1	-32.5	21.6	-52.2 (-30.7,-8.8) *	11.3	-63.8 (-42.2,-20.3) *
	8	45.1	-38.5	15.6	-58.3 (-32.1-7.4) *	8.5	-66.7 (-40.6,-15.8) *
	12	42.2	-41.4	15.5	-58.4 (-30.5,-3.4) *	8.3	-66.9 (-39.1,-11.8) *
Mean change from baseline in severity of MSVS	-2	2.5		2.5		2.5	
	4	2.3	-0.3	1.7	-0.8 (-0.8, -0.2)	1.2	-1.3 (-1.3, -0.8)
	8	2.1	-0.5	1.5	-0.9 (-0.8, -0.2)	0.9	-1.6 (-1.5, -0.8)
	12	2.0	-0.5	1.4	-1.1 (-0.8, -0.2)	0.9	-1.6 (-1.4, -0.7)
Mean percent change from baseline in the number of MSVS	-2	83.6		73.8		75.1	
	4		39.6	21.6	70.6 (-41.8, -20.3)	11.3	85.9 (-57.1, -35.5)
	8		47.5	15.6	77.5 (-41.0, -19.3)	8.5	89.3 (-52.7, -31.0)
	12		49.6	15.5	79.4 (-39.8, -29.9)	8.3	89.5 (-49.8, -29.9)

Source: Text Table pages 3258, 3260, 3262 of Vol. 108
* Statistically significance at 0.05 level.
Confidence intervals are calculated from 2-way ANOVA with factors for treatment and study center.

Treatment of Vulvovaginal Atrophy

The sponsor claimed subjects in the estradiol 0.05 mg/day or 0.10 mg/day groups who had signs or symptoms of vaginal atrophy at baseline had an overall trend toward improved measures of vaginal atrophy. This reviewer focuses only the sponsor's maturation index.

Maturation Index

The sponsor claimed that the mean changes from baseline to final evaluation for the maturation index for subjects with atrophy at baseline were significantly improved for estradiol 0.05 mg/day (p=0.008) and for estradiol 0.10 mg/day (p=0.003) as compared to placebo group (see Table 4).

Table 4
Mean Change from Baseline to Final Evaluation for the Maturation Index
Subjects with Atrophy at Baseline (ITT)

Visit	Placebo N=105	Estradiol 0.05 mg/day N=111	Estradiol 0.1 mg/day N=109
Baseline			
N (Number of Subjects with Atrophy)	20	21	19
Mean	30.6	32.2	29.6
Final Evaluation			
N(Number of Subjects with Atrophy)	21	21	19
Mean change from Baseline	21.3	41.2	42.2
P-value vs. Placebo		0.0008 *	0.003 *

Source: Text Table T-25: Page 3277 of Vol.108
* Denoted statistical significance at the 0.05 level using 2-way ANOVA with factors for treatment and study center

2.3.2 STATISTICAL REVIEWER'S FINDINGS

Table 5 presents this reviewer's efficacy endpoints. For the treatment of MSVS, the primary efficacy endpoint presented in the submission is the mean change from baseline in the number of MSVS between active and placebo groups at weeks 4 and 12. However, this is not in accordance with Division requirements for 4 co-primary efficacy endpoints, with hypothesis tests versus placebo for all four:

- mean change in the number of MSVS from baseline to week 4
- mean change in the number of MSVS from baseline to week 12
- mean change in the severity of MSVS from baseline to week 4
- mean change in the severity of MSVS from baseline to week 12.

For relieving urogenital symptoms, this reviewer focused on:

- mean change from baseline to final evaluation for the percentage of parabasal, intermediate, and superficial cells for subjects with atrophy
- mean change from baseline to final evaluation for the vaginal pH

Table 5
The reviewer's efficacy endpoints

Treatment of MSVS
Primary
• Mean change from baseline in the number of MSVS at weeks 4
• Mean change from baseline in the number of MSVS at weeks 12
• Mean change from baseline in the severity of MSVS at weeks 4
• Mean change from baseline in the severity of MSVS at weeks 12
Secondary
• Mean percent change from baseline in the number of MSVS at weeks 4, 8, and 12
Treatment of Urogenital Symptoms
• Mean change from baseline to final evaluation for the vaginal pH
• Mean percentage of Parabasal, intermediate, and superficial cells at baseline and final evaluation

Treatment of MSVS

For the treatment of MSVS, this reviewer's analyses are based on the ITT population from the sponsor's data sets submitted on April 2001. One placebo subject with 630 MSVS at baseline is excluded from the analysis as requested by the medical reviewer.

This reviewer's analysis of the mean changes from baseline in the number of MSVS at weeks 4 and 12 differs slightly from the sponsor's analysis because 1 placebo subject was excluded and the baseline was reduced from 83.6 to 78.4. This reviewer's confirmed the sponsor's MSVS obtained by the sponsor. Therefore, this reviewer's results agree with the sponsor's analyses.

The mean changes from baseline in the number of MSVS and in the severity of MSVS for the estradiol 0.05 mg/day and 0.10 mg/day groups were statistically different from the placebo group at weeks 4 and 12. This review analyzed the mean percent change from baseline in the number of MSVS. It produced similar results to that of the sponsor analysis.

Table 6 summarizes this reviewer's MSVS results. It includes adjusted 95% CI for treatment of MSVS at weeks 4, 8, and 12.

Table 6
Reviewer's MSVS Analyses
ITT and LOCF

Study Week		Placebo N=104	Estradiol 0.05 mg/day N=111	Estradiol 0.1 mg/day N=109
Mean Change from Baseline in the number of MSVS				
Baseline	Mean (SD) Range	78.4 (27.6)	73.8 (24.5)	75.1 (25.4)
4 #	Mean(SD) Mean change from Baseline(SD) P-value vs. Placebo (95%CI)	48.3(42.2) -30.0 (39.2)	21.6 (27.8) -52.2 (32.9) < 0.0001 (-32.3, -12.1)*	11.4 (19.4) -63.7 (26.7) < 0.0001 (-43.8, -23.6) *
8	Mean(SD) Mean change from Baseline(SD) (95%CI)	43.9 (40.3) -34.5 (39.0)	15.6 (23.2) -58.3 (31.4) (-33.9, -13.7)	8.4 (17.6) -66.7 (27.8) (-42.3, -22.1)
12 #	Mean(SD) Mean change from Baseline(SD) P-value vs. Placebo (95%CI)	42.2 (41.1)- 36.1 (36.6)	15.5 (25.4) -58.4 (31.4) <0.0001 (-30.4, -3.5) *	8.2 (16.6) -66.9 (27.4) < 0.0001 * (-39.0, -12.0) *
Mean Change from Baseline in the severity of MSVS				
Baseline	Mean (SD) Range	2.5 (0.26)	2.5 (0.23)	2.5 (0..3)
4 #	Actual mean(SD) Mean change from Baseline(SD) P-value vs. Placebo (95%CI)	2.23 (0.71) -0.28 (.69)	1.67 (1.07) -0.79 (1.08) =0.0001 (-0.81,-0.22)*	1.05 (1.14) -1.33 (1.0) < 0.0001 (-1.35, -0.75) *
8	Actual mean(SD) Mean change from Baseline(SD) (95% CI)	2.05 (0.92) -0.45 (0.91)	1.54 (1.15) -0.92 (1.13) (-0.79, -0.16)	0.87 (1.10) -1.61 (1.06) (-1.47, -0.83)
12 #	Actual mean(SD) Mean change from Baseline(SD) P-values (vs. Placebo) (95% CI	2.0 (0.96) - 0.51 (0.94)	1.41 (1.17) -1.06 (1.16) =0.0002 (-0.87, -0.23) *	0.87 (1.09) -1.6 (1.06) < 0.0001 (-1.3, -0.73) *
Mean Percent Change from Baseline in the number of MSVS				
Baseline	Mean (SD) Range)	78.4 (27.6)	73.8 (24.5)	75.1 (25.4)
4	Actual mean(SD) Mean change from Baseline(SD) (95%CI)	48.3 (42.4) 39.54 (42.9)	21.59 (27.76) 70.64 (37.57) (-41.9, -20.27)	11.37 (19.43) 85.9 (23.62) (-57.13, -35.5)
8	Actual mean(SD) Mean change from Baseline (SD) (95% CI)	43.89 (44.3) 47.23 (42.56)	15.56 (23.23) 77.59 (37.85) (-41.2, -19.48)	8.45 (17.55) 89.31 (22.18) (-53.0, -31.2)
12	Actual mean(SD) Mean change from Baseline(SD) (95% CI)	42.28 (41.32) 49.23 (41.11)	15.48 (25.42) 79.44 (33.61) (-40.14, -20.28)	8.25 (16.58) 89.54 (20.63) (-50.29, -30.34)

Source: SAS data
# Indicates the primary efficacy endpoint.
* Confidence intervals are adjusted for multiple pairwise comparison within each time point using Dunnett's method.

Subgroup Analysis of MSVS

This reviewer also performed exploratory subgroup analyses by age (<50, 50 to 59, > 59) using a 1-way ANOVA with treatment as factors for the mean change in the number of MSVS and the mean change in the severity of MSVS. The results of the subgroup analyses are presented in Table 7.

Table 7
Subgroup Analyses by Age
ITT and LOCF

Study Week	Age (years old)	Placebo N=104	Estradiol 0.05 mg/day N=111	Estradiol 0.1 mg/day N=109
Mean Change from Baseline in the number of MSVS				
4	< 50 (95% CI)	N=38 -30.6 (30.9)	N=27 -44.7 (37.9) (-33.3, 5.2)	N=37 -68.1 (34.1) (-55.2, 23.1) *
	50- 59 (95% CI)	N=59 -27.4 (41.4)	N=68 -55.2 (32.7) (-40.8, -14.7) *	N=59 -62.4 (22.2) (-48.5, -21.4) *
	> 59 (95% CI)	N=7 -49.1 (58.4)	N=16 -52.5 (23.1) (-36.3. 29.5)	N=13 -57.5 (20.5) (-42.5, 25.6)
8	< 50 (95% CI)	N=38 -33.5 (39.0)	N=27 -55.0 (34.1) (-40.0, -2.9) *	N=37 -70.6 (33.7) (-54.1, -20.0) *
	50- 59 (95% CI)	N=59 -33.1 (41.4)	N=68 -61.5 (31.0) (-41.6, -15.2) *	N=59 -65.5 (26) (-46.0, -18.7) *
	> 59 (95% CI)	N=7 -51.4 (57.0)	N=16 -50.2 (27.5) (-31.7, 33.9)	N=13 -60.8 (14.2) (-43.4, 24.4)
12	< 50 (95% CI)	N=38 -39.1 (30.5)	N=27 -54.8 (33.7) (-34, 2.5)	N=37 -70.5 (32.7) (-48.1, -14.7) *
	50- 59 lacebo (95% CI)	N=59 -32.5 (39.6)	N=68 -61.6 (30.5) (-42, -16.1) *	N=59 -66.3 (26.4) (-47.1, -20.4) *
	> 59 (95% CI)	N=7 -49.9 (42.1)	N=16 -50.7 (29.5) (-29.1, 27.6)	N=13 -59.2 (10.0) (-38.6, 20)
Mean Change from Baseline in Severity of MSVS				
4	< 50 (95% CI)	N=38 -0.3 (0.8)	N=27 -0.7 (1.0) (-0.93, 0.19)	N=37 -1.4 (1.1) (-1.563, -0.54) *
	50- 59 (95% CI)	N=59 -0.2 (0.5)	N=68 -0.8 (1.1)) (-0.95, -0.22) *	N=59 -1.3 (1.1) (-1.492, -0.73) *
	> 59 (95% CI)	N=7 -0.9 (1.3)	N=16 -1.1 (1.3) (-1.43, 1.05)	N=13 -1.4 (1.1) 411 (-1.76, 0.82)
8	< 50 (95% CI)	N=38 -0.6 (1.1)	N=27 -0.8 (1.1) (-0.76, 0.43) *	N=37 -1.7 (1.0) (-1.74, -0.64) *
	50- 59 (95% CI)	N=59 -0.3 (0.8)	N=68 -1.0 (1.1) (-1.01, -0.22) *	N=59 -1.6 (1.1) (-1.621, -0.80) *
	> 59 (95% CI)	N=7 -0.9 (1.2)	N=16 -1.1 (1.3) (-1.42, 1.02)	N=13 -1.4 (1.0) (-1.778, 0.74)
12	< 50 (95% CI)	N=38 -0.7 (1.1)	N=27 -0.8 (1.1) (-0.77, 0.49)	N=37 -1.5 (1.1) (-1.43, -0.28) *
	50- 59 (95% CI)	N=59 -0.4 (0.8)	N=68 -1.1 (1.2) (-1.1, -0.3) *	N=59 -1.5 (1.0) (-1.59, -0.75) *
	> 59 (95% CI)	N=7 -0.7 (1.0)	N=16 -1.3 (1.2) (-1.83, 0.55)	N=13 -1.7 (1.1) (-2.27, 0.19)

Source: SAS data
* Confidence intervals are adjusted for multiple pairwise comparison within each time point using Dunnett's method.

The mean change from baseline for age less than 50 years old showed improvement in the number and severity of MSVS for estradiol 0.10 mg/day at weeks 4, 8, and 12. However, the mean change from baseline for age less than 50 years old showed less or little improvement for estradiol 0.05 mg/day only appeared at week 8.

The mean change from baseline for age between 50 to 59 years old showed improvement in the number and severity of MSVS for both active treatment groups at weeks 4, 8, and 12.

The mean change from baseline for age greater than 59 years old showed little or no improvement in the number and severity of MSVS for both active treatment groups as compared to placebo at any time point.

Vaginal pH

Table 8 presents analysis of mean change from baseline to final evaluation for the vaginal pH. This table was provided from the sponsor dated September 15, 2002.

The mean change from baseline to final evaluation for vaginal pH showed statistically significance improvement the estradiol 0.05 mg/day (p=0.007). However, no statistically significant difference in the estradiol 0.10 mg/day (p=0.052).

Table 8
Analysis of Mean Change from Baseline to Final Evaluation for the vaginal pH

Study week	Placebo N=95		Estradiol 0.05 mg/day N=104		Estradiol 0.10 mg/day N=104	
	Mean	Mean change from Baseline	Mean	Mean change from Baseline	Mean	Mean change from Baseline
Baseline	5.32		5.33		5.32	
Final (P-value vs. Placebo)	5.07	-0.25	4.60	-0.73 (0.007) *	4.72	-0.60 0.052

Source: sponsor provided on September 15, 2002
* P-values are generated from a 1-way ANOVA with treatment as the factor.

Maturation Index

Table 9 presents the result the mean change from baseline to final evaluation for the percentage of parabasal, intermediate, and superficial cells for all treated subjects with atrophy. This reviewer calculated adjusted 95% confidence intervals and the maturation index, and added these results to the table.

In this table, only 63 in placebo, 58 in estradiol 0.05 mg/day, and 70 in estradiol 0.10 mg/day were available for analysis. At final evaluation, there were 15 in placebo, 31 in the estradiol 0.05 mg/day, and 22 subjects in the estradiol 0.10 mg/day which had been excluded from the analyses due to "cannot be performed: infection and/or inflammation". There were also 25, 22, and 17 subjects rejected in the Placebo, estradiol 0.05 mg/day, and estradiol 0.10 mg/day groups respectively for various other reasons.

The protocol required that each treatment group should have at least 85 subjects available for assessment after 12 weeks. The requirement of the protocol was not satisfied because only 63 in placebo, 58 in estradiol 0.05 mg/day, and 70 in estradiol 0.10 mg/day were available for analysis.

Table 9
Analysis of mean Change from Baseline to Final Evaluation for the Percentage of Parabasal, Intermediate, and Superficial cells for Subjects with Atrophy

		Placebo N=63		Estradiol 0.05 mg/day N=58		Estradiol 0.1 mg/day N=70	
	Study Week	Mean (SD)	Mean change from baseline	Mean (SD)	Mean change from baseline p-values versus placebo (95% CI)	Mean (SD)	Mean Change from baseline P-values vs. Placebo (95% CI)
Parabasal Cells (%)	Baseline	23.46 (37.5)		25.52 (37.5)		21.03 (36.7)	
(95% CI)	Final	15.16 (30.3)	-8.3	0.17 (1.3)	-25.34 (-32.6, -2.0) *	0.29 (2.4)	-20.74 (-27.3, 1.9)
Intermediate Cells (%)	Baseline	66.78 (32.1)		63.71 (31.6)		68.11 (32.5)	
(95% CI)	Final	73.97 (27.7)	7.19	73.02 (23.6)	9.31 (-13.8, 16.9)	69.93 (23.2)	1.81 (-20.5, 8.7)
Superficial Cells (%)	Baseline	9.76 (9.7)		10.78 (12.4)		10.86 (13.2)	
(95% CI)	Final	10.87 (13.7)	1.11	26.81 (23.7)	16.03 (6.0, 25.5)*	29.79 (23.5)	18.93 (9.3, 28.0)*
Maturation Index	Baseline	55.12 (17.8)		54.1 (18.4)		55.9 (17.8	
(95% CI)	Final	58.46 (15.0)	3.34	70.7 (9.6)	16.6 (5.0, 21.4) *	71.8 (9.6)	15.9 (4.7, 20.4) *

Source: Text Table provided from the sponsor on September 15, 2002.

- This reviewer used SAS data LAB_MI to exclude those subjects from "List of subjects excluded from maturation index analysis"provided on September 18, 2002
- This reviewer calculated the 95% confidence intervals using a 1-way ANOVA with treatment as the factor.

The difference between the two active treatment groups as compared to placebo are highly significant based on the percent superficial cells. At final evaluation, percent superficial cells increased from 10.8% to 26.8% (mean change=16%) in the estradiol 0.05 mg/day and from 10.9% to 29.8% (mean change=18.9%) in the estradiol 0.10 mg/day as compared to placebo (mean change =1.1%). For percent parabasal cells, there was a statistically significant reduction for the estradiol 0.05 mg/day from 25.5% to 0.2% (mean change=25.3%). However, there was no statistically significant reduction in the estradiol 0.10 mg/day reduced from 21% to 0.3% (mean change=20.7%) as compared to placebo group (mean change=8.3%). The maturation index showed statistically significance differences from all treated subjects with atrophy for both active groups when compared to placebo group. Note that increases in the superficial and intermediate cells and decreases parabasal cells are beneficial effects.

2.4 CONCLUSIONS

Subjects treated with estradiol 0.05 mg/day and 0.10 mg/day experienced statistically significant improvement in the number of MSVS and in the mean severity of MSVS as compared to placebo-treated subjects. A significant improvement in each active treatment group was detected at week 4, and maintained through weeks 8 and 12.

Subjects treated with estradiol 0.05 mg/day and 0.10 mg/day showed statistically significant increase in the percentage of superficial cells ($p < 0.001$). However, only subjects treated with estradiol 0.05 mg/day showed a statistically significant reduction in the percentage of parabasal cells. Note that increases in the superficial and intermediate cells and decreases

parabasal cells are beneficial effects. For vaginal pH, only subjects treated with estradiol 0.05 mg/day showed a statistically significant improvement.

2.5 LABELING COMMENTS

In accordance with Division requirements, the labeling should express 4 co-primary efficacy endpoints for the treatment of MSVS as shown below in the Table 10.

Table 10
Mean Change from Baseline of Moderate to Severe Vasomotor Symptoms in the Number and in Severity at weeks 4 and 12 Using LOCF (ITT Population)

Visit	Placebo (n=104)	Estradiol 0.05 mg/day (n=111)	Estradiol 0.10 mg/day (n=109)	Adjusted 95% CI * * Vs. Placebo	
				0.05 mg/day	0.10 mg/day
Baseline (in the number of MSVS)					
Mean (SD)	78.4 (27.4)	73.8 (24.5)	75.1(25.4)		
Week 4 (in the number of MSVS)					
Mean Change (SD)	-30.0 (39.2).	-52.2 (32.9) *	-63.7 (26.7) *	-32.3, -12.1	-43.8, -23.6
Week 12 (in the number of MSVS					
Mean change (SD)	-36.1 (36.6)	-58.4 31.4) *	-66.9 (27.4) *	-30.4, -3.5	-39.0, -12.0
Baseline (in the severity of MSVS)					
Mean (SD)	2.5 (0.26)	2.5 (0.23)	2.5 (0.3)		
Week 4 (in the severity of MSVS)					
Mean change (SD)	-0.3 (0.7)	-0.8 (1.1) *	-1.3 (1.0) *	-0.81, -0.22	-1.35, -0.75
Week 12 (in the severity of MSVS)					
Mean change (SD)	-0.5 (0.9)	-1.1 (1.2) *	-1.6 (1.1) *	-0.87, -0.23	-1.3, -0.73

* P<0.05 vs. Placebo

* * Confidence intervals (CI)are from a 2-way ANOVA with treatment group and study center as factors. CI are adjusted for multiple comparisons within each time point using Dunnett's method. A CI which excludes the value zero indicates the treatment group is significantly difference from placebo.

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