CENTER FOR DRUG EVALUATION AND RESEARCH

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Statistical Review(s)

U.S. Department of Health and Human Services
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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-633/N000
Drug Name:	Femtrace™ (Estradiol Acetate Tablets)
Indication(s):	1) Treatment of moderate-to-severe vasomotor symptoms, and 2) Treatment of vulvar and vaginal atrophy
Applicant:	Warner Chilcott Company, Inc.
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This NDA included two Phase 3 clinical trials (PR 00501 and PR 01502) to support the efficacy of Femtrace™ for the treatment of moderate-to-severe vasomotor symptoms (MSVS) and for the treatment of moderate to severe vulvar and vaginal atrophy (VVA) associated with the menopause. Subjects in study 00501 received estradiol acetate (EA) tablets containing 0.9 mg and 1.8 mg. Subjects in study PR 01502 received EA 0.45 mg.

For moderate-to-severe vasomotor symptoms, subjects treated with EA 0.45 mg, 0.9 mg and 1.8 mg showed both clinically and statistically significant change from baseline in frequency of MSVS as compared to placebo at weeks 4 and 12. Subjects treated with EA 0.9 mg and 1.8 mg showed a statistically significant change from baseline in severity compared to placebo at weeks 4 and 12. Subjects treated with EA 0.45 mg failed to show a statistically significant change in severity at week 4; however, a statistical difference was reached at week 7 but not maintained to week 12.

1.2 Brief Overview of Clinical Studies

Femtrace™ is an oral tablet containing estradiol acetate (EA), which is rapidly hydrolyzed to estradiol. The sponsor submitted two phase 3 studies (PR 00501 and PR 01502) to support the efficacy and safety of dosage strengths of estradiol acetate (EA) versus placebo for 12 weeks of treatment. These were double-blind, multicenter, parallel group studies. Study PR 00501 randomized 293 subjects to receive continuous administration of EA 0.9 mg, 1.8 mg, or placebo. Study PR 01502 enrolled 259 subjects to receive EA 0.45 mg or placebo. Table 1 summarizes these 2 studies. The proposed indications for Femtrace™ of these studies are:

- The treatment of moderate to severe vasomotor symptoms (MSVS) associated with the menopause, and
- The treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with the menopause.

1.3 Statistical Issues

The sponsor's primary analysis was based on ANOVA applied to change from baseline with terms for treatment, center, and treatment by center interaction. The reviewer applied ANCOVA with baseline as covariate as the latter approach reduces the variability of the estimated treatment effects. However, in analyzing the ANCOVA results, the reviewer found that the model residuals failed tests for normality, and thus a stratified Wilcoxon rank sum test was used as the basis for testing the significance of treatment effects. The reviewer's statistical analysis is consistent with recommendations for analysis currently provided to sponsors for the proposed indications.

The EA 0.45 mg dose study shows a statistically significant difference from placebo in mean change from baseline in frequency at weeks 4 and 12. Differences from placebo are consistently shown for the intervening weekly intervals. A statistically significant difference from placebo in the mean change from baseline in the severity score is not achieved until week 7; however, the weekly differences are not consistently maintained to week 12, although significance is shown at week 12. The results are similar for both the ITT and the modified ITT* populations (with 24 subjects excluded).

To further explore low-dose treatment effects, the sponsor performed a responder analyses based on the proportion of subjects who experienced 75% or greater reduction in symptoms. Compared to placebo, a statistical difference is shown for frequency for each week, 5 through 12 and for severity at weeks 6 through 12, except for weeks 7 and 9. This finding indicates that a 75 % reduction in the severity of MSVS is not consistently maintained through week 12, which is consistent with results based on mean change scores. Analyses based on responders should be considered exploratory and for descriptive purposes only and should not be supportive of any labeling for this indication.

2. INTRODUCTION

2.1 Overview

Femtrace™ is an oral tablet containing estradiol acetate (EA), which is rapidly hydrolyzed to estradiol. Two phase 3 studies PR 00501 and PR 01502 were submitted for review. These 2 studies were double-blind, multicenter, parallel group studies in which healthy postmenopausal women were randomized to receive EA 0.45 mg, 0.9 mg, 1.8 mg EA, or placebo for 12 weeks of treatment (see Table 1).

The primary objective of these studies was to determine the efficacy of daily administration of EA compared with placebo in decreasing in the number and severity of hot flushes in postmenopausal women. The secondary objectives were to evaluate the efficacy of treatment in relieving urogenital symptoms. Subjects ages 36 to 80 years who had undergone surgically menopausal (hysterectomy with or without bilateral oophorectomy greater than 6 weeks prior to randomization) and experienced at least 7 moderate or severe hot flushes per day, or an average of 60 per week during the two-week baseline screening period were eligible for these studies. Patients recorded vasomotor symptoms on daily diary cards during the baseline and treatment periods. MSVS scores were 0=no flushes, 1=mild, 2=moderate, and 3=severe.

Table 1
Summary of Controlled Trial

Study Number/ Report Study Period	Trial Design	Center/# of Sites	Treatment Group	Duration	Number Enrolled/Complete
PR 00501/ RR 033020.0 10/2001 – 11/2002	Double-blind, randomized, multicenter, placebo-controlled, parallel group	U.S./44	0.9 mg/day 1.8 mg/day Placebo	12 Weeks	293/263
PR 01502/ RR 03402.0 6/2002 – 2/2003	Double-blind, randomized, multicenter, placebo-controlled, parallel group	U.S./40	0.45 mg Placebo	12 Weeks	259/221

Source: Adapted from Volume 36, page 4039

2.1.1 Study PR 00501

Study PR 00501 was a multicenter, randomized, placebo controlled trial, parallel group study conducted in 44 U.S. centers (three of these centers were initiated but did not enroll any subjects) for a total of 293 healthy postmenopausal women to the following 3 treatments groups: 100 subjects in the EA 0.9 mg group; 98 subjects in the EA 1.8 mg group; and 95 subjects in the placebo group. A total of 263 subjects who completed the study with 12 weeks of treatment.

2.1.2 Study PR 01502

Study PR 01502 was a multicenter, randomized, placebo controlled trial, parallel group study conducted in 40 U.S. centers (four of these centers were initiated but did not enroll any subjects) for a total of 259 healthy postmenopausal women to the following 2 treatments groups: 132 subjects in the EA 0.45 mg group and 127 subjects in the placebo group. There were 218 women who completed the study with 12 weeks of treatment.

In this study, medication labels were mistakenly unblinded for 24 women randomized at site 62 (see Amendment 1). The sponsor defined all efficacy analyses based on ITT* excluding those 24 subjects from Site 62, and 14 subjects from the Intent-to-Treat (ITT) population with no post-baseline observations. The ITT* population included 221 subjects, 113 subjects in the EA 0.45 mg group and 108 subjects in the placebo group (see Table 2).

2.1.3 Patient Disposition, Demographic and Baseline Characteristics

For study PR 00501, a total of 263 subjects completed the study with 12 weeks of treatment; 88 (88%) subjects in the EA 0.9 mg; 90 (95%) subjects in the EA 1.8 mg group; and 85 (90%) subjects in the placebo group. The primary reason for discontinuing was lack of efficacy (2.8%) for all treatment groups. The overall mean age was 53.4 (range: 41 to 68 years), mean height was 64.0 inches and mean weight was 165 pounds. The majority of participants were Caucasian (78%). Approximately 10% of the subjects did not complete the 12 weeks of treatment (see Table 2).

For study PR 01502, a total of 218 subjects completed 12 weeks of treatment; 116 (88%) subjects in the EA 0.45 mg, and 102 (80%) subjects in the placebo group. The primary reasons for discontinuing were lack of efficacy (5.4%) and lost to follow-up (5.7%) for all treatment groups. The overall, mean age was 52.2 years (range: 36 to 80 years), mean height was 63.9 inches, and mean weight 164 was pounds. The majority of participants were Caucasian (80%). Approximately over 20% of the subjects did not complete the 12 weeks of treatment (see Table 2).

The sponsor claimed that these studies showed no significant differences with respect to demographic and baseline characteristics among treatment groups.

Table 2
Subject withdrawal by Treatment Group

	Study PR 00501			Study PR 01502	
	Placebo	**EA 0.9 mg**	**EA 1.8 mg**	**Placebo**	**EA 0.45 mg**
Number of subjects in ITT	94	100	95	127	132
Number (%) of Subjects completed the Study	85 (90 %)	88 (88 %)	90 (95 %)	102 (80 %)	116 (88%)
Number (%) of subjects who did not completed study	10 (11%)	12 (12%)	8 (8%)	25 (20 %)	16 (12%)
Adverse event	2 (2 %)	4 (4 %)	1 (1 %)	4 (3 %)	0 (0 %)
Lake of efficacy	4 (4 %)	2 (2 %)	2 (2 %)	9 (7 %)	5 (4 %)
Lost to follow-up	2 (2 %)	2 (2 %)	3 (3 %)	7 (6 %)	8 (6 %)
Withdrew consent	1 (1 %)	2 (2 %)	1 (1 %)	4 (3 %)	1 (0.8 %)
Protocol violation	0 (0 %)	1 (1 %)	0 (0 %)	-	-
Other	1 (1 %)	1 (1 %)	1 (1 %)	1 (1 %)	1 (0.8 %)
Death	-*	-	-	0 (0 %)	1 (0.8%)

Source: Adapted from PR 00501, Volumes 77, Text Table 14.1.2, and adapted from PR 01502, Volume 93, Text Table 14.1.2
All percentage are based on the number of subjects randomized to each treatment group.
*: no data available

2.2 Data Sources

This NDA was submitted in volume document form on October 14, 2003. The SAS data sets were submitted electronically and were located on \\cdsesub1\N21663\N_000\2003-10-14. Additional data sets regarding the efficacy endpoints of MSVS and VVA were requested on December 8, 2003 and received on December 16, 2003, and August 2, 2004.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The sponsor used analysis of variance (ANOVA) model with effects of treatment, center, and treatment-by-center interaction performed for each of the target variables at each post-treatment week as planned in the protocol. The treatment-by-center interaction was dropped from the model if the interaction term was not significant. All efficacy analyses were based on an intent-to-treat (ITT) population and a modified intent-to-treat (ITT*). The ITT is defined as all subjects randomized who took at least 1 dose of study drug and who had at least 1 observation after dosing. The modified ITT* included all ITT population excluding those 24 subjects inadvertently unblinded from study PR 01502, and excluding 14 subjects without a post-baseline observation. The sponsor used the last observation carried forward (LOCF) approach to estimate missing data in the most recent non-missing evaluation. In order to achieve minimal cell sizes for analysis, centers with fewer than 12 subjects were pooled by geographic region. The sponsor also performed age subgroup analyses (< 50 years, 50-59, and ≥ 60 years).

This reviewer applied an analysis of covariance (ANCOVA) for the efficacy analysis. The variables included baseline, treatment, center, and treatment-by-center interaction. The treatment-by-center interaction was dropped from the model if it showed no significance ($p > 0.05$). A Shipiro-Wilkes test was applied to evaluate the residuals for the normality assumption. If the normality assumption was not valid, re-analysis using a stratified Wilcoxon rank sum test (Van Elteren test) with center as the stratification variable was performed.

The tabulated results present the least squares mean change from baseline with standard error. The 95% confidence interval (CI) was based on the difference between the least squares mean estimate for each treatment versus placebo groups. However, since the data did not meet the normality assumption, all p-values are based on the Wilcoxon rank sum test.

Effects on Vasomotor Symptoms

For treatment of moderate-to-severe vasomotor symptoms (MSVS), the efficacy may be demonstrated by both a clinically and a statistically significant reduction in the number and in the severity of hot flushes in the treated groups compared to the placebo group. This reduction in the number and in the severity of hot flushes should occur within 4 weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment. The study should identify the lowest effective dose to support the indication. The treatment group should be significantly better than placebo for all four co-primary endpoints as follows:

- Mean change from baseline in number of MSVS at week 4
- Mean change from baseline in number of MSVS at week 12
- Mean change from baseline in severity of MSVS at week 4
- Mean change from baseline in severity of MSVS at week 12

  severity is defined as SS1 = (2*nr_mod + 3*nr_sev) / nr_ms

  where nr_mod and nr_sev are the numbers of moderate and severe hot flushes, and

  nr_ms = nr_mod + nr_sev is the total number of moderate to severe hot flushes.

Effects on Vulvar and Vaginal Atrophy

[ ]

[ ]

3.2 Results for Moderate-to-Severe Vasomotor Symptoms (MSVS) Indication

The sponsor used ANOVA with factors for treatment, center, and treatment-by-center interaction. Subjects treated with the lowest dose EA 0.45 mg showed that the mean change from baseline in the number first achieved statistical significance at week 6, and showed that the mean change in the severity first achieved statistical significance at week 5. Significant reduction was maintained to week 12 (see Tables 31 & 32 in the appendix). Subjects treated with EA 0.9 mg and 1.8 mg showed that the mean changes from baseline in the number and in the severity of MSVS were statistically significant as compared to the placebo group at weeks 4 and 12 (see Tables 29 & 30 in the appendix). This reviewer was able to replicate the sponsor's MSVS results.

Study PR 00501

This reviewer used an ANCOVA model with baseline, treatment, center, and treatment-by-center interaction. The placebo group had a higher mean number of MSVS (86.1) compared to the EA 0.9 mg (78.5) and the 1.8 mg (82.4) at baseline (see Table 3). Subjects treated with EA 0.9 mg and EA 1.8 mg showed statistical significance in the number and in the severity of MSVS at weeks 4 and 12 ($p < 0.001$) as compared to placebo group (see Tables 3 & 4). Significant reduction these 2 treatment groups were detected at week 4, and was maintained to week 12. EA 0.9 mg and 1.8 mg demonstrated a clinically significant difference of 2 or more MSVS per day (or 14 per week). The EA 1.8 mg demonstrated a slightly stronger initial reduction in MSVS than EA 0.9 mg, from a baseline of 11.8/day down to 3.1/day, and 11.2/day down to 3.5/day, respectively at week 4.

Table 3
Study PR 00501
Mean Change from Baseline in the Number of MSVS per week in the ITT[a] Population using LOCF[b] Analysis

Week	Placebo (N=94)	Femtrace 0.9 mg (N=100)	Femtrace 1.8 mg (N=95)
Baseline [1]			
Mean (SD)	86.1 (40.2)	78.5 (24.9)	82.4 (39.1)
Week 4*			
Mean (SD)	51.5 (47.2)	24.3 (28.4)	21.9 (25.9)
Mean (SE) change from baseline	-30.1 (3.3)	-56.5 (3.2)	-59.3 (3.4)
95% CI Femtrace – Placebo		(-35.5, -17.4)	(-38.5, -19.8)
P-values [2]		< 0.001	< 0.001
Week 8			
Mean (SD)	46.1 (51.6)	19.2 (29.4)	9.3 (15.5)
Mean (SE) change from baseline	-37.4 (3.4)	-62.5 (3.3)	-73.3 (3.4)
95% CI Femtrace – Placebo		(-25.1, -34.5)	(-35.9, -45.3)
Week 12*			
Mean (SD)	46.8 (54.6)	17.5 (28.9)	7.3 (15.2)
Mean (SE) change from baseline	-36.3 (3.5)	-63.9 (3.4)	-74.8 (3.6)
95% CI Femtrace – Placebo		(-37.3, -17.9)	(-48.5, -28.5)
P-values [2]		< 0.001	< 0.001

Sources: SAS dataset
[a]ITT=Intent-to-Treat, [b]LOCF=Last Observation Carried Forward
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
* : Primary endpoint
[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-weeek between screening and randomization
[2]: P-values based on Wilcoxon rank sum test (van Elteren's test)

Table 4
Study PR 00501
Mean Change from Baseline in the Severity of MSVS per week in the ITT[a] Population using LOCF[b] Analysis

Week	Placebo (N=94)	Femtrace 0.9 mg (N=100)	Femtrace 1.8 mg (N=95)
Baseline [1]			
Mean (SD)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)
Week 4*			
Mean (SD)	2.3 (0.6)	1.8 (1.0)	1.9 (1.0)
Mean (SE) change from baseline	-0.2 (1.0)	-0.7 (0.1)	-0.7 (0.1)
95% CI Femtrace – Placebo		(-0.8, -0.2)	(-0.7, -0.2)
P-values [2]		0.001	0.002
Week 8			
Mean (SD)	2.2 (0.8)	1.5 (1.2)	1.2 (1.2)
Mean (SE) change from baseline	-0.3 (0.1)	-1.0 (0.1)	-1.3 (0.1)
95% CI Femtrace – Placebo		(-1.0, -0.4)	(-1.2, -0.6)
Week 12*			
Mean (SD)	2.2 (0.8)	1.4 (1.2)	1.0 (1.2)
Mean (SE) change from baseline	-0.3 (0.1)	-1.1 (0.1)	-1.5 (0.1)
95% CI Femtrace – Placebo		(-1.1, -0.5)	(-1.5, -0.9)
P-values [2]		< 0.001	<0.001

Sources: SAS dataset
[a]ITT=Intent-to-Treat, [b]LOCF=Last Observation Carried Forward
Mean change is ANCOVA adjusted mean change. Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
* : Primary endpoint
[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-weeek between screening and randomization
[2]: P-values based on Wilcoxon rank sum test (Van Elteren test)
Change from baseline in the severity defined as SS1 = (2*nr_mod + 3*nr_sev) / nr_ms
Where nr_ms = nr_mod + nr_sev is the total number of moderate to severe hot flushes.

Study PR 01502 based on modified ITT* population (with 24 subjects excluded)

Subjects treated with EA 0.45 mg showed a mean change from baseline in the number of MSVS statistically significant at week 4 (p=0.014) and week 12 (p=0.005) as compared to placebo group (see Table 5). However, the mean change from baseline in the severity was not statistically significant at week 4 (p=0.787) (see Table 6), but was significant at week 12 (p=0.016) as compared to placebo group. This reviewer analyzed the mean change from baseline in the severity of total hot flushes (including mild); this was also not significant at week 4 (p=0.216) (see Table 7).

The discrepancy in this reviewer's analyses of the mean change in the number of MSVS showed significance at week 4 (p=0.014 with ranked data ANCOVA). The sponsor's analyses showed no statistical significance (p=0.113 with raw-data ANOVA) (see Table 31).

Table 5
Study PR 01502
Mean Change from Baseline in the Number of MSVS per week in the ITT* (with exclusion)[a] using LOCF[b] Analysis

Week	Placebo (N=108)	Femtrace 0.45 mg (N=113)
Baseline [1] Mean (SD)	85.8 (37.8)	86.2 (34.8)
Week 4*		
Mean (SD)	51.5 (37.1)	44.1 (39.5)
Mean (SE) change from baseline	-33.8 (3.5)	-41.5 (3.5)
95% CI Femtrace – Placebo		(-17.3, 1.9)
P-values [2]		0.014
Week 8		
Mean (SD)	45.7 (36.8)	35.9 (39.8)
Mean (SE) change from baseline	-39.4 (3.4)	-49.5 (3.4)
95% CI Femtrace - Placebo		(-19.5, -0.7)
Week 12*		
Mean (SD)	43.1 (38.1)	34.1 (40.9)
Mean (SE) change from baseline	-41.5 (3.5)	-51.2 (3.5)
95% CI Femtrace – Placebo		(-19.5, 0.07)
P-values [2]		0.005

Sources: SAS dataset
[a]ITT* (with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[b]LOCF=Last Observation Carried Forward.
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval.
* : Primary endpoint
[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-weeek between screening and randomization
[2]: P-values based on Wilcoxon rank sum test (Van Elteren test)

Table 6
Study PR 01502
Mean Change from Baseline in the Severity of MSVS per week in the ITT* (with exclusion)[a] using LOCF[b] Analysis

Week	Placebo (N=108)	Femtrace 0.45 mg (N=113)
Baseline [1]		
Mean (SD)	2.6 (0.2)	2.5 (0.2)
Week 4*		
Mean (SD)	2.4 (0.5)	2.3 (0.7)
Mean (SE) change from baseline	-0.2 (0.1)	-0.3 (0.06)
95% CI Femtrace – Placebo		(-0.3, 0.05)
P-values [2]		0.787
Week 8		
Mean (SD)	2.4 (0.6)	2.1 (0.9)
Mean (SE) change from baseline	-0.2 (0.07)	-0.5 (0.07)
95% CI Femtrace – Placebo		(-0.6, -0.2)
Week 12*		
Mean (SD)	2.3 (0.8)	1.9 (1.1)
Mean (SE) change from baseline	-0.3 (0.1)	-0.7 (0.1)
95% CI Femtrace – Placebo		(-0.7, -0.2)
P-values [2]		0.016

Sources: SAS dataset
[a]ITT*(with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[b]LOCF=Last Observation Carried Forward.
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
* : Primary endpoint
[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-weeek between screening and randomization
[2]:P-values based on Wilcoxon rank sum test (Van Elteren test)
Change from baseline in the severity defined as SS1 = (2*nr_mod + 3*nr_sev) / nr_ms
where nr_mod and nr_sev were the numbers of moderate and severe hot flushes, and
nr_ms = nr_mod + nr_sev was the total number of moderate to severe hot flushes.

Table 7
Study PR 01502
Mean Change from Baseline in the Severity of Total Hot Flushes† per week in the ITT* (with exclusion)[a] using LOCF[b] Analysis

Week	Placebo (N=108)	Femtrace 0.45 mg (N=113)
Baseline [1]		
Mean (SD)	2.4 (0.3)	2.4 (0.3)
Week 4*		
Mean (SD)	2.2 (0.5)	2.1 (0.6)
Mean (SE) change from baseline	-0.2 (0.05)	-0.3 (0.05)
95% CI Femtrace – Placebo		(-0.2, 0.04)
P-values [2]		0.216
Week 8		
Mean (SD)	2.2 (0.6)	1.9 (0.8)
Mean (SE) change from baseline	-0.2 (0.06)	-0.5 (0.06)
95% CI Femtrace – Placebo		(-0.5, -0.1)
Week 12*		
Mean (SD)	2.1 (0.7)	1.7 (0.9)
Mean (SE) change from baseline	-0.3 (0.08)	-0.6 (0.08)
95% CI Femtrace – Placebo		(-0.6, -0.1)
P-values [2]		0.031

Sources: SAS dataset
[a]ITT* (with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[b]LOCF=Last Observation Carried Forward.
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
†: total hot flushes (sum of mild, moderate or severe hot flushes)
* : Primary endpoint
[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-weeek between screening and randomization
[2]: P-values based on Wilcoxon rank sum test (Van Elteren test)
Change from baseline in the severity defined as SS2 = (nr_mild + 2*nr_mod + 3*nr_sev) / nr_total where nr_mild, nr_mod and nr_sev were the numbers of mild, moderate and severe hot flushes, respectively, and nr_total was the total number of all hot flushes.

Study PR 01502 based on modified ITT* population (with 24 subjects excluded) at each study week

Since the mean change from baseline compared to placebo in the severity of MSVS did not show statistical significance at week 4, results for each subsequent week were investigated as an exploratory sensitivity analysis. The mean change from baseline in the severity, Femtrace versus placebo, showed significance at weeks 7, 8, 11 and 12 (see Table 9), but not at weeks 9 and 10. Note that the lowest dose showed the reduction in the severity of hot flushes occurred at week 7, however, did not maintain statistical significance through week 12 on this modified ITT* population.

Table 8
Study PR 01502
Mean change from baseline in the number of moderate to severe hot flushes at each study week using LOCF[a] (ITT* Population, ANCOVA)

Study Visit	Placebo (N=108)	EA 0.45 mg (N=113)	p-value (95% CI Femtrace – Placebo) [1]
Baseline			
Mean (SD)	85.8 (37.8)	86.2 (34.8)	
Week 1			
Mean change (SE)	-18.3 (2.8)	-20.5 (2.8)	0.155 (-10.1, 5.5)
Week 2			
Mean change (SE)	-26.0 (3.3)	-29.7 (3.3)	0.122 (-12.9, 5.4)
Week 3			
Mean change (SE)	-30.6 (3.5)	-35.6 (3.4)	0.032 (-15.6, -3.5)
Week 4 *			
Mean change (SE)	-33.8 (3.5)	-41.5 (3.4)	0.014 (-17.3, -1.9)
Week 5			
Mean change (SE)	-35.2 (3.5)	-44.1 (3.5)	0.007 (-18.5, -2.9)
Week 6			
Mean change (SE)	-36.2 (3.4)	-46.8 (3.4)	0.001 (-20.0, -4.1)
Week 7			
Mean change (SE)	-37.4 (3.5)	-46.3 (3.5)	0.004 (-18.5, -2.7)
Week 8 *			
Mean change (SE)	-39.3 (3.4)	-49.5 (3.4)	0.001 (-19.5, -4.7)
Week 9			
Mean change (SE)	-39.8 (3.5)	-50.5 (3.4)	0.002 (-20.2, -4.1)
Week 10			
Mean change (SE)	-41.4 (3.5)	-51.0 (3.5)	0.003 (-19.2, -4.1)
Week 11			
Mean change (SE)	-41.6 (3.5)	-51.0 (3.5)	0.006 (-19.1, -3.3)
Week 12 *			
Mean change (SE)	-41.5 (3.5)	-51.2 (3.5)	0.005 (-19.5, -4.1)

Sources: SAS dataset received on 8/2/04
ITT*(with exclusion): exclude 24 subjects inadvertently unblinded at site 62.
[a]LOCF=Last Observation Carried Forward.
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI Confidence Interval
*: primary endpoint
Statistically significance at 0.05 level is marked gray
[1]:P-values based on Wilcoxon rank sum test (Van Elteren test)

Table 9
Study PR 01502
Mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF[a] (ITT* Population, ANCOVA)

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-value (95% CI Femtrace – Placebo) [1]
Baseline Mean (SD)	2.6 (0.2)	2.5 (0.2)	
Week 1 Mean change (SE)	0.002 (0.01)	-0.02 (0.01)	0.898 (-0.05, 0.1)
Week 2 Mean change (SE)	-0.08 (0.04)	-0.1 (0.03)	0.370 (-0.13, 0.1)
Week 3 Mean change (SE)	-0.1 (0.04)	-0.1 (0.04)	0.239 (-0.1, 0.08)
Week 4 * Mean change (SE)	-0.2(0.06)	-0.3 (0.06)	0.787 (-0.3, 0.05)
Week 5 Mean change (SE)	-0.1 (0.06)	-0.4 (0.06)	0.204 (-0.4, -0.05)
Week 6 Mean change (SE)	-0.2 (0.08)	-0.5 (0.08)	0.223 (-0.5, -0.1)
Week 7 Mean change (SE)	-0.2 (0.08)	-0.5 (0.08)	0.050 (-0.5, -0.05)
Week 8 * Mean change (SE)	-0.2 (0.07)	-0.5 (0.07)	0.006 (-0.6, -0.1)
Week 9 Mean change (SE)	-0.2 (0.08)	-0.5 (0.08)	0.063 (-0.5, -0.06)
Week 10 Mean change (SE)	-0.3 (0.08)	-0.6 (0.08)	0.107 (-0.5, -0.06)
Week 11 Mean change (SE)	-0.2 (0.09)	-0.7 (0.08)	0.010 (-0.7, -0.3)
Week 12 * Mean change (SE)	-0.3 (0.09)	-0.7 (0.09)	0.016 (-0.7, -0.2)

Sources: SAS dataset received on 8/4/04
ITT*(with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[a]LOCF=Last Observation Carried Forward.
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
*: primary endpoint, statistically significance at 0.05 level is marked gray
[1]:P-values based on Wilcoxon rank sum test (Van Elteren test)
Change from baseline in the severity defined as SS1 = (2*nr_mod + 3*nr_sev) / nr_ms
where nr_mod and nr_sev were the numbers of moderate and severe hot flushes, and
nr_ms = nr_mod + nr_sev was the total number of moderate to severe hot flushes

Study PR 01502 based on ITT population at each study week

This reviewer also analyzed those 24 subjects inadvertently unblinded from study site 62, the results in mean changes from baseline in the number and in the severity of MSVS, Femtrace versus placebo, were similar with the modified ITT* population (see Tables 8 & 9). EA 0.45 mg showed a statistically significant difference from placebo at week 6; however, the result was not consistently maintained to week 12 for ITT population.

Table 10
Study PR 01502
Mean change from baseline in the number of moderate to severe hot flushes at each study week using LOCF[a] (ITT Population, ANCOVA)

Study Visit	Placebo (n=120)	EA 0.45 mg (n=125)	p-value (95% CI Femtrace – Placebo) [1]
Baseline			
Mean (SD)	84.5 (36.5)	85.1 (33.5)	
Week 1			
Mean (SE) change	-19.2 (2.7)	-20.9 (2.6)	0.196 (-8.9, 5.6)
Week 2			
Mean change (SE)	-26.3 (3.1)	-29.5 (3.3)	0.131 (-11.7, 5.3)
Week 3			
Mean change (SE)	-29.7 (3.2)	-35.1 (3.2)	0.034 (-14.2, -3.4)
Week 4 *			
Mean change (SE)	-33.5 (3.2)	-40.6 (3.2)	0.016 (-15.9, 1.8)
Week 5			
Mean change (SE)	-35.0 (3.2)	-43.4 (3.2)	0.004 (-17.3, 0.5)
Week 6			
Mean change (SE)	-36.1 (3.2)	-46.1 (3.1)	<0.001 (-18.7, -1.4)
Week 7			
Mean change (SE)	-37.0 (3.2)	-45.8 (3.2)	0.002 (-17.7, -0.07)
Week 8 *			
Mean change (SE)	-39.0 (3.2)	-49.1 (3.1)	<0.001 (-18.7, -1.4)
Week 9			
Mean change (SE)	-39.5 (3.2)	-50.1 (3.1)	0.001 (-19.3, -1.8)
Week 10			
Mean change (SE)	-41.4 (3.2)	-50.6 (3.2)	0.002 (-18.0, -0.3)
Week 11			
Mean change (SE)	-41.5 (3.2)	-50.7 (3.2)	0.003 (-18.1, -0.3)
Week 12 *			
Mean change (SE)	-42.0 (3.3)	-51.1 (3.5)	0.005 (-18.0, -0.1)

Sources: SAS dataset received on 8/2/04
ITT: Intent-to-Treat population
[a]LOCF=Last Observation Carried Forward.
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
*: primary endpoint, statistically significance at 0.05 level is marked gray
[1]:P-values based on Wilcoxon rank sum test (Van Elteren test)

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Table 11
Study PR 01502
Mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF[a] (ITT Population, ANCOVA)

Study Visit	Placebo (n=120)	EA 0.45 mg (n=125)	p-value (95% CI Femtrace – Placebo) [1]
Baseline Mean (SD)	2.4 (0.3)	2.4 (0.3)	
Week 1 Mean (SE) change	-0.03 (0.02)	-0.09 (0.02)	0.225 (-0.12, 0.01)
Week 2 Mean change (SE)	-0.1 (0.04)	-0.2 (0.04)	0.407 (-0.15, 0.05)
Week 3 Mean change (SE)	-0.2 (0.04)	-0.2 (0.04)	0.741 (-0.2, 0.06)
Week 4 * Mean change (SE)	-0.3(0.05)	-0.2 (0.05)	0.181 (-0.3, 0.02)
Week 5 Mean change (SE)	-0.4 (0.05)	-0.2 (0.05)	0.108 (-0.3, -0.07)
Week 6 Mean change (SE)	-0.4 (0.05)	-0.2 (0.05)	0.018 (-0.4, -0.04)
Week 7 Mean change (SE)	-0.3 (0.06)	-0.4 (0.06)	0.027 (-0.3, -0.003)
Week 8 * Mean change (SE)	-0.2 (0.06)	-0.5 (0.06)	0.012 (-0.4, -0.1)
Week 9 Mean change (SE)	-0.3 (0.06)	-0.5 (0.06)	0.027 (-0.4, -0.03)
Week 10 Mean change (SE)	-0.3 (0.06)	-0.5 (0.06)	0.175 (-0.4, -0.004)
Week 11 Mean change (SE)	-0.3 (0.07)	-0.6 (0.07)	0.015 (-0.5, -0.1)
Week 12 * Mean change (SE)	-0.3 (0.07)	-0.6 (0.07)	0.055 (-0.5, -0.1)

Sources: SAS dataset received on 8/4/04
ITT: Intent-to-Treat,[a]LOCF=Last Observation Carried Forward
Mean change is ANCOVA adjusted mean change.
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI -Confidence Interval
*: primary endpoint, statistically significance at 0.05 level is marked gray
[1]:P-values based on Wilcoxon rank sum test (Van Elteren test)
Change from baseline in the severity defined as SSI – (2*nr_mod + 3*nr_sev) / nr_ms
where nr_mod and nr_sev were the numbers of moderate and severe hot flushes, and
nr_ms = nr_mod + nr_sev was the total number of moderate to severe hot flushes.

3. Responder Analysis

The sponsor submitted a post hoc analysis due to the modest effect of the EA 0.45 mg dose in reducing the moderate-to-severe hot flushes symptoms (see Amendment 13). This analysis determined differences in responder rates between the lowest dose EA 0.45 mg and the placebo groups. The sponsor defined "responder" rates as any subject with a 75% or greater decrease from baseline in weekly frequency of moderate-to-severe hot flushes. That was based on the mean percent decrease in the weekly frequency of moderate-to-severe hot flushes from baseline to week 12 for the EA 0.9 mg treatment group was 77.7%.

Table 12 shows the proportion of subjects who experienced 75% or more reduction in the severity of MSVS. For the 75% reduction threshold in the severity of MSVS, the EA 0.45 mg showed significance at weeks 6, 8, 10, 11, and 12 but not at weeks 7 and 9; this finding showed that 75 % reduction in the severity of MSVS do not maintain statistical significance through week 12. This result was consistent with the analysis for the mean change in the severity.

Table 12
Number of Subjects with 75% or more with Reduction in the Severity of MSVS in the ITT* (with exclusion)[a]

Week	Treatment	Severity		
		N	# response	P-values*
3	EA 0.45 mg	113	4 (3.5%)	0.370
	Placebo	108	1 (0.9%)	
4	EA 0.45 mg	113	8 (7.1%)	0.216
	Placebo	108	3 (2.8%)	
5	EA 0.45 mg	113	11 (9.7%)	0.051
	Placebo	108	3 (2.8%)	
6	EA 0.45 mg	113	17 (15.0%)	0.012
	Placebo	108	5 (4.6%)	
7	EA 0.45 mg	113	17 (15.0%)	0.090
	Placebo	108	8 (7.4%)	
8	EA 0.45 mg	113	17 (15.0%)	0.012
	Placebo	108	5 (4.6%)	
9	EA 0.45 mg	113	16 (14.2%)	0.131
	Placebo	108	8 (7.4%)	
10	EA 0.45 mg	113	20 (17.7%)	0.047
	Placebo	108	9 (8.3%)	
11	EA 0.45 mg	113	26 (23.0%)	<0.001
	Placebo	108	7 (6.5%)	
12	EA 0.45 mg	113	27 (23.9%)	0.004
	Placebo	108	10 (9.3%)	

Source: documents received by facsimile on July 23, 2004
[a]ITT*(with exclusion):exclude 24 subjects inadvertently unblinded
* : P-values were exploratory and calculated from Fisher's Exact test
Statistically significance at 0.05 level is marked gray

The choice of the percent reduction threshold is arbitrary. There is no present consensus as to what constitutes a clinically meaningful magnitude for percent reduction, and what differences between placebo and drug in percent reduction (effect size) should be clinically relevant. These analyses should considered as exploratory and should not be support any labeling for this endpoint.

Reviewer's conclusion for indication of MSVS

For moderate-to-severe vasomotor symptoms, subjects treated with 0.9 mg and 1.8 mg showed both clinical and statistical significant change from baseline in the number of MSVS as compared to placebo at weeks 4 and 12. Subjects treated with EA 0.9 mg and 1.8 mg showed statistical significant change from baseline compared to placebo in the severity at weeks 4 and 12.

Subject treated with EA 0.45 mg showed statistical significant change from baseline in the number of MSVS as compared to placebo at weeks 4 and 12. However, it failed to show a statistically significant difference in the severity from placebo at week 4; a statistical difference was reached by week 7, however, the weekly results through week 12 were not consistently significant.

Tables 13 and 14 summarize the results of the p-values based on the sponsor's ANOVA analyses and this FDA reviewer's rank-based analyses on the modified ITT* (with 24 subjects excluded) and the ITT population. There were discrepancy of the sponsor's and this reviewer's results in the mean changes in the number and in the severity of MSVS, for Femtrace compared to placebo. However, this FDA reviewer's non-parametric analysis is more appropriate as shown below. The mean change from baseline in the severity of MSVS, Femtrace versus placebo, did not show consistent results of statistical significance to week 12 on both modified ITT*, ITT populations, and75% reduction threshold in the severity of MSVS.

Table 13
Study PR 01502 (EA 0.45 mg)
Mean change from baseline of moderate to severe hot flushes at each study week using LOCF[a]
ITT*(with exclusion), p-values [1], Femtrace versus Placebo

Study Visit	In Frequency[c]		In Severity[d]	
	Sponsor[e]	FDA Reviewer[f]	Sponsor[e]	FDA Reviewer[f]
Week 4	0.113	0.014	0.259	0.787
Week 5	0.076	0.007	0.010	0.204
Week 6	0.042	0.001	0.006	0.223
Week 7	0.094	0.004	0.025	0.050
Week 8	0.048	0.001	<0.001	0.006
Week 9	0.038	0.002	0.012	0.063
Week 10	0.064	0.003	0.015	0.107
Week 11	0.058	0.006	<0.001	0.010
Week 12	0.049	0.005	<0.001	0.016

[a]LOCF=Last Observation Carried Forward, [b]ITT*: exclude 24 subjects at site 62
[c]In Frequency= Mean change from baseline in frequency of MSVS, Femtrace versus Placebo
[d]In Severity= Mean change from baseline in severity of MSVS, Femtrace versus Placebo
[e]: Sponsor's analysis, [f]: FDA statistician analysis
[1]:P-values obtained from the sponsor's result was based on ANOVA model, while the reviewer's results were based on an ANCOVA model with p-values based on the Wilcoxon rank sum test

Table 14
Study PR 01502 (EA 0.45 mg)
Mean change from baseline of moderate to severe hot flushes at each study week using LOCF[a] ITT[b] Population, p-values [1], Femtrace versus Placebo

Study Visit	In Frequency[c]		In Severity[d]	
	Sponsor[e]	FDA Reviewer[f]	Sponsor[e]	FDA Reviewer[f]
Week 4	0.167	0.016	0.188	0.181
Week 5	0.100	0.003	0.020	0.108
Week 6	0.047	0.001	0.004	0.018
Week 7	0.081	0.002	0.027	0.027
Week 8	0.049	0.001	0.002	0.012
Week 9	0.043	0.001	0.042	0.027
Week 10	0.079	0.002	0.023	0.175
Week 11	0.086	0.003	0.001	0.015
Week 12	0.095	0.005	0.006	0.055

[a]LOCF=Last Observation Carried Forward, [b]ITT: Intent-to-Treat,
[c]In Frequency= Mean change from baseline in number of MSVS, Femtrace versus Placebo
[d]In Severity= Mean change from baseline in severity of MSVS, Femtrace versus Placebo
[e]: Sponsor's analysis, [f]: FDA statistician analysis
[1]:P-values obtained from the sponsor's result was based on ANOVA model, while the reviewer's results were based on an ANCOVA model with p-values based on the Wilcoxon rank sum test

3.3 Results for Treatment of Vulvar and Vaginal Atrophy (VVA) Indication

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age

Tables 25-28 presented the sponsor's subgroup analyses by age (<50, 50-59, > 60) using a 1-way ANOVA with treatment as factor.

In the 50 to 59 year age group, EA 0.9 mg and 1.8 mg showed statistically significance change from baseline in the number and in the severity of MSVS as compared to placebo at weeks 4. This result was observed at week 12. (see Tables 25 & 26). Subjects treated with EA 0.45 mg showed a statistically significant change from baseline, compared to placebo, in the mean of MSVS frequency at weeks 4 and 12. (see Table 27). However, statistical significance for change in severity is noted for weeks 5 and 12 (see Table 28).

Subjects less than 50 years treated with EA 1.8 mg showed a statistically significant change from baseline in the MSVS frequency at week 4 and week 12, but no significant change in the severity score was occurred.

The subgroup > 60 years had too few subjects to perform assessment of treatment effect.

Table 25
Study PR 00501
Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms By week, ITT[a] Population using LOCF[b]

	Week	Placebo	EA 0.9 mg	EA 1.8 mg
Age < 50 years				
Baseline Mean (Standard Deviation (SD))		86.8 (30.4) N=24	78.5 (23.7) N=24	86.6 (60.7) N=23
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo P-values vs. Placebo [1]	4*	51.2 (34.4) -35.6 (38.2)	27.3 (26.1) -51.2 (25.8) (-30.1, -9.04) 0.232	23.4 (21.0) -63.2 (62.9) (-37.8, -14.0) < 0.001
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo	8	40.9 (38.4) -45.9 (42.2)	29.3 (38.3) -49.3 (26.9) (-30.7, -7.98)	11.2 (13.5) -75.4 (64.4) (-45.9, -20.3)
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo P-values vs. Placebo [1]	12*	42.7 (52.6) -44.1 (55.1)	26.5 (36.2) -52.0 (27.4) (-33.9, -9.47) < 0.001	9.4 (15.7) -77.2 (64.8) (-49.1, -22.3) < 0.001
Age 50 – 59 years				
Baseline Mean (SD)		85.5 (46.7) N=59	77.7 (24.0) N=65	82.2 (30.3) N=67
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo P-values vs. Placebo [1]	4*	52.3 (54.1) -33.2 (47.5)	22.8 (29.6) -54.9 (29.3) (-30.1, -9.04) 0.001	22.7 (27.9) -59.5 (30.5) (-37.8, -14.0) < 0.001
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo	8	48.3 (57.9) -37.2 (51.8)	16.4 (27.0) -61.2 (31.3) (-30.1, -9.04) < 0.001	9.3 (16.6) -72.9 (32.1) (-37.8, -14.0) < 0.001
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo P-values vs. Placebo [1]	12*	48.4 (58.1) -37.1 (54.8)	14.8 (27.1) -62.9 (32.5) (-30.7, -7.98) < 0.001	7.2 (15.5) -75.0 (29.4) (-45.9, -20.3) < 0.001
Age > 60 years				
Baseline Mean (S) N		88.1 (17.1) N=11	83.6 (33.2) N=11	65.6 (12.2) N=5
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo P-values vs. Placebo [1]	4*	47.9 (31.7) -40.2 (27.3)	26.7 (27.6) -56.9 (48.5) (-30.1, -9.04) 0.296	3.6 (4.8) -62.0 (15.7) (-37.8, -14.0) 0.280
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo	8	45.8 (43.1) -42.3 (33.6)	13.6 (12.8) -70.0 (39.0) (-30.1, -9.04)	0.0 (0.0) -65.6 (12.1) (-37.8, -14.0)
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo P-values vs. Placebo [1]	12*	47.2 (42.3) -41.0 (31.7)	13.5 (16.8) -70.0 (37.6) (-30.7, -7.98) 0.044	0.0 (0.0) -65.6 (12.1) (-37.8, -14.0) 0.168

Source: Adapted from Volume 77, Text Tables 14.2.17, 14.2.19, 14.2.21
[a]ITT: Intent-to-Treat, [b]LOCF=Last Observation Carried Forward, CI=Confidence Interval, SD=Standard Deviation
P-values based on Fisher's Test
*: Secondary endpoint

Table 26
Study PR 00501
Mean Change from Baseline in the Severity of Moderate to Severe Vasomotor Symptoms
By week, ITT[a] Population using LOCF[b]

	Week	Placebo	EA 0.9mg	EA 1.8 mg
Age < 50 years				
Baseline Mean (Standard Deviation (SD))		2.5 (0.2) N=24	2.5 (0.2) N=24	2.5 (0.3) N=23
Mean (SD)	4*	2.3 (0.8)	2.0 (0.8)	2.0 (0.8)
Mean (SD) change from baseline		-0.3 (0.8)	-0.5 (0.9)	-0.5 (0.9)
95% CI vs. Placebo			(-0.72, -0.24)	(-0.71, -0.22)
P-values vs. Placebo [1]			0.385	0.303
Mean (SD)	8	1.9 (1.0)	1.6 (1.1)	1.4 (1.2)
Mean (SD) change from baseline		-0.6 (1.1)	-0.9 (1.2)	-1.1 (1.3)
95% CI vs. Placebo			(-0.96, -0.39)	(-1.22, -0.63)
Mean (SD)	12*	2.0 (1.1)	1.4 (1.2)	1.3 (1.2)
Mean (SD) change from baseline		-0.6 (1.1)	-1.1 (1.2)	-1.2 (1.3)
95% CI vs. Placebo			(-1.1, -0.52)	(-1.46, -0.88)
P-values vs. Placebo [1]			0.149	0.082
Age 50 – 59 years				
Baseline Mean (SD)		2.5 (0.2) N=59	2.5 (0.2) N=65	2.5 (0.3) N=67
Mean (SD)	4*	2.3 (0.7)	1.6 (1.1)	1.7 (1.1)
Mean (SD) change from baseline		-0.2 (0.7)	-0.9 (1.1)	-0.8 (1.1)
95% CI vs. Placebo			(-0.72, -0.24)	(-0.71, -0.22)
P-values vs. Placebo [1]			< 0.001	0.005
Mean (SD)	8	2.0 (1.0)	1.1 (1.2)	1.2 (1.1)
Mean (SD) change from baseline		-0.5 (1.0)	-1.4 (1.2)	-1.3 (1.2)
95% CI vs. Placebo			(-0.96, -0.39)	(-1.22, -0.63)
Mean (SD)	12*	1.9 (1.0)	0.9 (1.2)	0.8 (1.1)
Mean (SD) change from baseline		-0.6 (1.0)	-1.6 (1.2)	-1.7 (1.1)
95% CI vs. Placebo			(-1.1, -0.52)	(-1.46, -0.88)
P-values vs. Placebo [1]			< 0.001	< 0.001
Age > 60 years				
Baseline Mean (SD)		2.5 (0.2) N=11	2.5 (0.3) N=11	2.5 (0.1) N=5
Mean (SD)	4*	2.2 (0.8)	1.7 (1.1)	1.5 (1.4)
Mean (SD) change from baseline		-0.3 (0.7)	-0.8 (1.2)	-1.0 (1.4)
95% CI vs. Placebo			(-0.72, -0.24)	(-0.71, -0.22)
P-values vs. Placebo [1]			0.253	0.198
Mean (SD)	8	1.7 (1.1)	1.6 (1.3)	0.0 (0.0)
Mean (SD) change from baseline		-0.7 (1.0)	-0.9 (1.2)	-2.5 (0.1)
95% CI vs. Placebo			(-0.96, -0.39)	(-1.22, -0.63)
Mean (SD)	12*	1.5 (1.2)	1.4 (1.2)	0.0 (0.0)
Mean (SD) change from baseline		-0.9 (1.2)	-1.1 (1.1)	-2.5 (0.1)
95% CI vs. Placebo			(-1.1, -0.52)	(-1.46, -0.88)
P-values vs. Placebo [1]			0.793	0.008*

Source: Adapted from Volume 77, Text Tables 14.2.23, 14.2.25 14.2.27
[a]ITT: Intent-to-Treat, [b]LOCF=Last Observation Carried Forward, CI=Confidence Interval, SD=Standard Deviation
P-values based on Fisher's Test
*: Secondary endpoints

Table 27
Study PR 01502
Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms
By week, ITT*(with exclusion)[a] using LOCF[b]

	Week	Placebo	EA 0.45 mg
Age < 50 years			
Baseline Mean (SD)		88.47 (49.3) N=39	88.76 (31.5) N=33
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	4*	45.8 (34.3) -42.6 (60.9)	49.4 (39.1) -39.3 (42.1) 0.794
Mean (SD) Mean (SD) change from baseline	8	39.9 (34.1) -48.6 (58.4)	49.4 (43.5) -39.3 (44.3)
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	12*	37.0 (36.4) -51.5 (58.2)	45.5 (45.0) -43.3 (46.2) 0.516
Age 50 – 59 years			
Baseline Mean (SD)		82.7 (29.7) N=60	84.6 (35.3) N=66
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	4*	55.3 (38.0) -27.4 (39.1)	42.7 (38.6) -41.9 (26.9) 0.016
Mean (SD) Mean (SD) change from baseline	8	50.8 (38.9) -31.9 (39.3)	31.3 (37.1) -53.3 (27.4)
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	12*	48.2 (39.4) -34.5 (41.6)	30.3 (38.0) -54.3 (28.3) 0.002
Age > 60 years			
Baseline Mean (SD)		95.28 (30.3) N=9	88.0 (41.7) N=14
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo [1]	4*	50.9 (43.4) -44.4 (61.3)	38.5 (45.5) -49.5 (42.5) 0.815
Mean (SD) Mean (SD) change from baseline	8	37.6 (31.3) -57.7 (49.0)	25.4 (37.8) -62.6 (41.6)
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	12*	34.9 (34.3) -60.4 (48.1)	25.0 (41.2) -63.0 (41.8) 0.891

Source: Adapted from Volume 93, Text Tables 14.2.17, 14.2.19 14.2.21
[a]ITT* (with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[b]LOCF=Last Observation Carried Forward, CI=Confidence Interval, SD=Standard Deviation
P-values based on Fisher's Test
*: Secondary endpoints

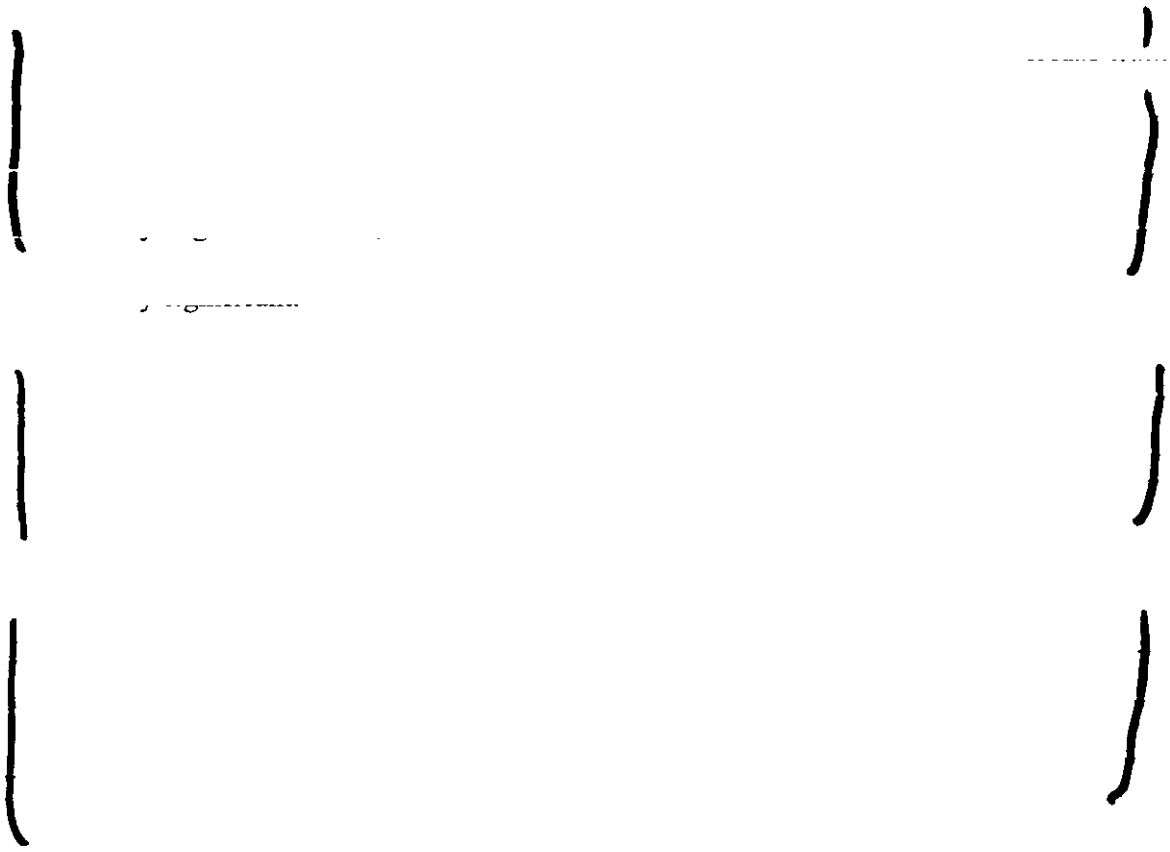
Table 28
Study PR 01502
Mean Change from Baseline in the Severity of Moderate to Severe Vasomotor Symptoms
By week, ITT*(with exclusion)[a] using LOCF[b]

	Week	Placebo	EA 0.45 mg
Age < 50 years			
Baseline Mean (SD)		2.6 (0.2) N=39	2.5 (0.2) N=33
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	4*	2.3 (0.6) -0.2 (0.6)	2.2 (0.7) -0.3 (0.7) 0.804
Mean (SD) Mean (SD) change from baseline	8	2.4 (0.6) -0.2 (0.6)	2.1 (0.8) -0.3 (0.8)
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	12*	2.1 (1.0) -0.4 (1.0)	2.0 (0.9) -0.5 (0.9) 0.787
Age 50 -59 years			
Baseline Mean(SD)		2.5 (0.2) N=60	2.6 (0.2) N=66
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	4*	2.5 (0.3) -0.1 (0.2)	2.3 (0.7) -0.2 (0.7) 0.074
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	5	2.5 (0.3) -0.1 (0.2)	2.3 (0.8) -0.3 (0.8) 0.018
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	8	2.4 (0.5) -0.1 (0.5)	2.1 (0.9) -0.5 (0.9) 0.005
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	12*	2.4 (0.6) -0.2 (0.6)	1.8 (1.1) -0.7 (1.1) < 0.001
Age > 60 years			
Baseline Mean (SD)		2.6 (0.2) N=9	2.6 (0.2) N=14
Mean (SD) Mean (SD) change from baseline 95% CI vs. Placebo [1]	4*	2.2 (0.9) -0.4 (1.0)	2.2 (0.7) -0.3 (0.7) 0.749
Mean (SD) Mean (SD) change from baseline	8	2.2 (0.9) -0.4 (1.0)	1.7 (1.2) -0.8 (1.2)
Mean (SD) Mean (SD) change from baseline P-values vs. Placebo [1]	12*	2.2 (0.9) -0.4 (1.0)	1.6 (1.3) -1.0 (1.2) 0.243

Source: Adapted from Volume 93, Text Tables 14.2.23, 14.2.25 14.2.27
[a]ITT* (with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[b]LOCF=Last Observation Carried Forward, CI=Confidence Interval, SD=Standard Deviation
P-values based on Fisher's Test
*: Secondary endpoint

5. SUMMARY AND CONCLUSIONS

For moderate-to-severe vasomotor symptoms, subjects treated with EA 0.45 mg, 0.9 mg and 1.8 mg showed both clinically and statistically significant change from baseline in frequency of MSVS as compared to placebo at weeks 4 and 12. Subjects treated with EA 0.9 mg and 1.8 mg showed a statistically significant change from baseline in severity compared to placebo at weeks 4 and 12. Subjects treated with EA 0.45 mg failed to show a statistically significant change in severity at week 4; however, a statistical difference was reached at week 7 but not maintained to week 12.



Labeling Comments

Consistent with labeling for similar products, the primary efficacy results can be expressed in terms of mean values and standard errors obtained from the least squares estimates. The p-values should be footnoted as being based on the Wilcoxon rank sum test. Results from this reviewer's Tables 3 to 6 may be used as appropriate. For the MSVS indication, the labeling should indicate statistical significance, as appropriate, for only the co-primary endpoints at week 4 and week 12.

APPENDICES

Table 29
Study PR 00501
Sponsor's Mean Change in the Number of MSVS Analyses By week, ITT[a] Population using LOCF[b]

Week	Placebo (N=94)	Femtrace 0.9 mg (N=100)	Femtrace 1.8 mg (N=95)
Baseline [1] Mean (SD)	86.1 (40.2)	78.5 (24.9)	82.4 (39.1)
Week 4*			
Mean (SD)	51.5 (47.2) -	24.3 (28.4)	21.9 (25.9)
Mean (SD) change from baseline	-34.6 (43.0)	-54.2 (30.8)	-60.5 (39.9)
95% CI Femtrace - Placebo		(-30.1, -9.04)	(-37.8, -14.0)
P-values		< 0.001	< 0.001
Week 8			
Mean (SD)	46.1 (51.6)	19.2 (29.4)	9.3 (15.5)
Mean (SD) change from baseline	-40.0 (47.4)	-59.3 (31.5)	-73.1 (41.3)
95% CI Femtrace - Placebo		(-30.7, -7.98)	(-45.9, -20.3)
Week 12*			
Mean (SD)	46.8 (54.6)	17.5 (28.9)	7.3 (15.2)
Mean (SD) change from baseline	-39.3 (52.3)	-61.0 (32.1)	-75.0 (40.0)
95% CI Femtrace - Placebo		(-33.9, -9.47)	(-49.1, -22.3)
P-values		< 0.001	< 0.001

Source: Adapted from Study PR 00501, Final Study Report, Section 11.4.1.1.1.1, Text Table 11.
[a]ITT=Intent-to-Treat, [b]LOCF=Last Observation Carried Forward.
Mean=Arithmetic Mean, SD=Standard Deviation, CI=Confidence Interval
*: Primary endpoint
[1]: The baseline in number of MSVS was the weekly average number of MSVS during the 2-weeek between screening and randomization

Table 30
Study PR 00501
Sponsor's Mean Change in the Severity of MSVS Analyses By week, ITT[a] Population using LOCF[b]

	Placebo (N=94)	Femtrace 0.9 mg (N=100)	Femtrace 1.8 mg (N=95)
Baseline [1] Mean (SD)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)
Week 4*			
Mean (SD)	2.3 (0.6)	1.8 (1.0)	1.9 (1.0)
Mean (SD) change from baseline	-0.2 (0.6)	-0.7 (1.0)	-0.7 (1.0)
95% CI Femtrace - Placebo		(-0.72, -0.24)	(-0.71, -0.22)
P-values		0.003	< 0.001
Week 8			
Mean (SD)	2.2 (0.8)	1.5 (1.2)	1.2 (1.2)
Mean (SD) change from baseline	-0.3 (0.8)	-1.0 (1.1)	-1.3 (1.2)
95% CI Femtrace - Placebo		(-0.96, -0.39)	(-1.22, -0.63)
Week 12*			
Mean (SD)	2.2 (0.8)	1.4 (1.2)	1.0 (1.2)
Mean (SD) change from baseline	2.3 (0.8)	-1.1 (1.2)	-1.5 (1.2)
95% CI Femtrace - Placebo		(-1.1, -0.52)	(-1.46, -0.88)
P-values		< 0.001	< 0.001

Source: Adapted from Study PR 00501, Final Study Report, Section 11.4.1.1.1.1, Text Table 11.
[a]ITT=Intent-to-Treat, [b]LOCF=Last Observation Carried Forward,
Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval
*: Primary endpoint
[1]: The baseline in number of MSVS was the weekly average number of MSVS during the 2-weeek between screening and randomization

Table 31
Study PR 01502
Sponsor's Mean Change in the Number of MSVS Analyses at each study week,
ITT* (with exclusion)[a] using LOCF[b]

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	P-values (Femtrace-Placebo)
Baseline Mean (SD)	85.8 (37.8)	86.2 (34.3)	
Week 4 *			
Mean Change (SD)	-34.3 (50.0)	-42.1 (33.8)	0.113
Week 5			
Mean Change (SD)	-35.8 (50.2)	-44.8 (34.5)	0.076
Week 6			
Mean Change (SD)	-36.8 (49.2)	-47.5 (33.8)	0.042
Week 7			
Mean Change (SD)	-38.1 (49.4)	-47.2 (35.2)	0.094
Week 8			
Mean Change (SD)	-40.1 (48.3)	-50.4 (35.4)	0.048
Week 9			
Mean Change (SD)	-40.7 (48.6)	-51.4 (31.4)	0.038
Week 10			
Mean Change (SD)	-42.3 (49.1)	-51.8 (31.6)	0.064
Week 11			
Mean Change (SD)	-42.8 (48.7)	-51.9 (31.6)	0.058
Week 12 *			
Mean Change (SD)	-42.8 (49.2)	-52.2 (36.3)	0.049

Source: Adapted from Study PR 01502, Final Study Report, Section 11.4.1.1.1.1, Text Table 11 and Volume 53, Page 11050, Table 14.2.1
[a]ITT* (with exclusion): intent-to-treat but excluding Site 62, [b]LOCF = last observation carried forward
*: Primary endpoint, statistically significance at 0.05 level is marked gray

Table 32
Study PR 01502
Sponsor's Mean Change from Baseline in the Severity of MSVS Analyses at each study week,
ITT* (with exclusion)[a] using LOCF[b]

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	P-values (Femtrace – Placebo)
Baseline Mean (SD)	2.6 (0.2)	2.5 (0.2)	
Week 4 *			0.259
Mean Change (SD)	-0.2 (0.5)	-0.3 (0.7)	
Week 5			
Mean Change (SD)	-0.1 (0.5)	-0.3 (0.8)	0.010
Week 6			
Mean Change (SD)	-0.2 (0.6)	-0.5 (0.9)	0.006
Week 7			
Mean Change (SD)	-0.2 (0.7)	-0.5 (0.9)	0.025
Week 8			
Mean Change (SD)	-0.2 (0.6)	-0.5 (0.9)	< 0.001
Week 9			
Mean Change (SD)	-0.2 (0.7)	-0.5 (0.9)	0.012
Week 10			
Mean Change (SD)	-0.3 (0.8)	-0.5 (1.0)	0.015
Week 11			
Mean Change (SD)	-0.2 (0.7)	-0.7 (1.1)	< 0.001
Week 12 *			
Mean Change (SD)	-0.3 (0.8)	-0.7 (1.1)	< 0.001

Source: Adapted from Study PR 01502 Final Study Report, Section 11.4.1.1.2.1, Text Table 13.
[a]ITT* (with exclusion): intent-to-treat but excluding Site 62, [b]LOCF = last observation carried forward
*: Primary endpoint, statistically significance at 0.05 level is marked gray

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Mike Welch
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Concur with review.

S. Edward Nevius
8/17/04 05:17:38 PM
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Concur with review.

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 21-633/S-000

Applicant: Galen (Chemicals) Limits

Trade/Generic Name: Femtrace™

Indication: Treatment of moderate-to-severe vasomotor symptoms and treatment of vulvar and vaginal atrophy,

Date of Submission: October 20, 2003

Filing Date: December 2, 2003

User Fee Goal Date: August 20, 2004

Project Manager: Dale Cutright (HFD-580)

Medical Reviewer: Theresa Van der Vlugt, M.D. (HFD-580)

Screened by: Moh-Jee Ng, M.S. (HFD-715)

Comments: This NDA is fileable from a statistical perspective.

Please provide efficacy analysis data sets, data definition files in SAS transport format, and also include SAS source code used for the analyses above and any supporting output.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	Access to EDR data OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	OK

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