U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Transitional Science
Office of Biostatistics

Addendum to the Statistical Review

NDA/Serial Number:	22-038
Drug Name:	Divigel® (Estradiol Gel, 0.1%) 0.25 g, 0.5 g and 1 g Strength
Indication(s):	Treatment of Moderate to Severe Vasomotor Symptoms (b) (4) Associated with the Menopause
Applicant:	Upsher-Smith Laboratories, Inc.
Date(s):	
Submission:	May 05, 2006
User Fee Goal:	March, 05, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Ling Chen, Ph.D. Mathematical Statistician, HFD 705
Concurring Reviewers:	Mahboob Sobhan, Ph.D. Statistical Team Leader
Medical Division:	Division of Reproductive and Urologic Drug Products
Clinical Team:	Audrey Gassman, M.D. - Shelley Slaughter, M.D.
Project Manager:	George Lyght

Keywords:
NDA Review, Clinical Trial, Multi-Center, Randomization

This is an amendment to the statistical review. The second paragraph of section 1.1 should read “Based on the data submitted, this reviewer’s analysis showed that daily regimens of Divigel 1.0 g and 0.5 g doses were statistically significant ($p<.001$ and $p<.05$, respectively) in the reductions of the median daily frequency of moderate to severe vasomotor symptoms at week 4, and maintained through week 12. The reductions in the median daily severity of symptoms were also statistically significant ($p<.001$) at week 4, and maintained through week 12. The 0.25 g dose of Divigel, however, did not show statistically significant reductions in both median daily frequency and severity until weeks 5 and 7, respectively”.

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/s/

Mahboob Sobhan
6/5/2007 04:03:00 PM
BIOMETRICS

U.S. Department of Health and Human Services
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Statistical Review and Evaluation

CLINICAL STUDIES

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Table of Contents

TABLE OF TABLES

TABLE OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant, Upsher-Smith Laboratories, Inc., seek approval for Divigel® in the treatment of moderate to severe vasomotor symptoms (VMS) (b) (4) associated with menopause. To support the above indications, the applicant reports the efficacy and safety data from a single randomized, double-blind, multicenter study (P04-001) study. Three daily dosing regimens of Divigel® (1.0 g, 0.5 g, and 0.25 g) were compared to placebo in this study.

Based on the data submitted, this reviewer's analysis showed that daily regimens of Divigel® 1.0 g and 0.5 g doses were statistically significant in the reductions of the median daily frequency and severity ($p \leq 0.11$ and $p < 0.001$, respectively) of moderate to severe vasomotor symptoms from baseline to week 4 when compared to placebo, and maintained through week 12. The 0.25 g dose of Divigel®, however, did not show statistically significant reductions until week 5 and 7 for the daily frequency and severity, respectively.

(b) (4)

From statistical perspective, this study demonstrates that both 1.0 g and 0.5 g of Divigel® were efficacious per guidance criteria in treating moderate to severe vasomotor symptoms associated with menopause.

1.2 Brief Overview of Clinical Studies

Study P04-001 was a randomized, parallel, placebo-controlled, double-blind, prospective multicenter phase 3 study in postmenopausal women with moderate to severe vasomotor symptoms (MSVS). Placebo or one of three Divigel® doses (0.25 g, 0.5 g, or 1.0 g) were administered topically once daily for a period of 12 week period. A total of 495 subjects from 48 sites in the USA and Canada participated in this study.

The primary objective of Study P04-001 was to compare the change in mean daily frequency and mean daily severity of MSVS between three doses of Divigel® (0.25 g, 0.5 g and 1.0 g) and placebo from baseline to week 4 and 12.

(b) (4)

(b) (4)

1.3 Statistical Issues and Findings

The clinical and statistical review team has identified data alterations (changes in dates, symptoms scores etc.) in several source diaries (patient diary) supplied by the applicant from three study sites. These changes were deemed questionable in regards to data integrity. To evaluate the severity of the problem, source documents from few more randomly selected sites were reviewed by the clinical reviewer. Additional data alterations, mostly changes in dates and crossed out numbers, were noted in these additional source diaries, but it appeared the integrity of the efficacy data was not compromised to affect the efficacy conclusions. Details of these alterations can be found in clinical reviewer's report.

In addition, this reviewer also found issues in data handling rules such as definition of ITT population, LOCF imputation method and rules of dealing with blanks in vasomotor symptom diary and issues with the responder analysis (see Section 5.1).

(b) (4)

Despite suboptimal study conduct noted above, the study demonstrated the efficacy for Divigel® 1.0 g and 0.5 g doses but not for 0.25 g dose in the treatment of moderate to severe vasomotor symptoms.

2. INTRODUCTION

Estradiol Gel, 0.1% was approved and marketed in some other countries with labeled daily doses of 0.5 g and 1.0 g of estradiol applied topically. While these doses were appropriate for most women, it was expected that some women would get adequate symptomatic relief from daily dose of 0.25 g estradiol per day. It was also expected that some women who may initially need the higher dose levels will receive satisfactory treatment with lower doses as their menopause progresses and that the dose level could be titrated downwards to the lowest effective dose. Because of the outcome of the Women's Health Initiative (WHI), the recommendation for treatment with female hormones was to use the lowest effective dose; therefore, the protocol included the 0.25 g/day estradiol dose level to determine what proportion of women received symptomatic relief from this lower dose. It was intended that this lower dose could be included in the label for the subset of women who receive satisfactory treatment and could be used in titrating women to a lower dose as menopause progresses.

2.1 Overview of Study P04-001

Study P04-001 was a randomized, parallel, placebo-controlled, double-blind, prospective multicenter phase 3 study in postmenopausal women with MSVS. Placebo or one of three Divigel® doses (0.25 g, 0.5 g, or 1.0 g) were administered topically once daily for the 12 week period. A total of 495 subjects from 48 sites in the USA and Canada participated in this study.

The primary objective was to compare the change from baseline in mean daily frequency and severity of moderate to severe vasomotor symptoms (MSVS) at weeks 4 and 12 between Divigel® and placebo.

The secondary objective was to assess the effect of Divigel® versus placebo on vulvar and vaginal atrophy (VVA): specifically – the change in the moderate to severe symptom identified as most bothersome by the patient. However, due to small number of subjects who met the Division's criteria for such an analysis, this reviewer did not perform any further evaluation of VVA.

In addition, the Sponsor examined a "Responder" analysis, where a patient was defined as responder if the patient experienced at least a 50% reduction in the daily frequency of MSVS from baseline. Since the responder analysis conducted by the Sponsor was only based on the two of the four co-primary endpoints for MSVS indication, the results from the Sponsor's responder analysis can not be used to support the efficacy results from the primary analysis for MSVS indication.

2.2 Data Sources

The Sponsor provided the SAS data electronically, and the study report in paper version as well as in electronic format. The electronic data is located at \\Cdsesub1\n22038\N_000\2006-05-01.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy for MSVS Indication

3.1.1 Study Design and Endpoints

3.1.1.1 Study design

This was a randomized, parallel, placebo-controlled, double-blind, multicenter study in postmenopausal women with MSVS. Patients received treatment with Divigel® (Estradiol Gel, 0.1%) or placebo for 12 weeks. This study consisted of a screening period, four study visits (Visits 2-5) for patients without an intact uterus, and five study visits (Visit 2-6) for patients with a uterus. For patients who required a washout from current hormone therapy, the screening period included a 4-week to 6-month washout period depending on the hormone therapy being discontinued. Prior to randomization, patients completed the symptom diary for at least 12 days, which provided baseline data for the efficacy analyses. Patients who met the eligibility criteria during the screening evaluations were randomized to one of the following four treatment groups: Divigel® 0.25 g, 0.5 g, 1.0 g, or matching placebo gel. All patients applied the study drug topically to the thigh once daily, alternating between the left and right thigh daily, for 12 weeks.

3.1.1.2 Efficacy Endpoints

As per protocol, the following endpoints were considered co-primary:

- Change in mean daily frequency of MSVS from baseline to week 4 and 12; and
- Change in mean daily severity of MSVS from baseline to week 4 and 12.

The mean daily frequency (or severity) is referred to the average daily frequency (or severity) in a week for a subject. For avoiding the confusion with population mean, this reviewer omitted the "mean" in the definition of primary endpoints in this report.

3.1.2 Study Population

3.1.2.1 Patient disposition

Of 1070 screened patients, 495 patients were randomized as follows: 125 (25.3%) in Divigel® 1.0 g, 123 (24.8%) in Divigel® 0.5 g, 122 (24.6%) in Divigel® 0.25 g, and 125 (25.3%) in placebo group. All of the 495 randomized patients received study drug according to the randomization scheme and were, therefore, evaluable for safety. Of the 495 treated patients, 488 (98.6%) provided at least four days of diary data in at least one post-baseline week (protocol defined ITT population). Data listed in Table 1 (Part of Sponsor's Listing 6.2.2) identifies patients excluded from the ITT population.

Table 1: Reason for Exclusion from ITT Population

Investigator/ Patient No./ Age/Race	Treatment	Reason(s) for Exclusion
2931/ 56/ White	Divigel® 1.0 g	No post-baseline diary weeks with at least 4 days of diary data
2947/ 51/ Other	Divigel® 0.25 g	No post-baseline diary data
4209/ 40/ White	Placebo	No post-baseline diary weeks with at least 4 days of diary data
4213/ 60/ White	Divigel® 0.5 g	No post-baseline diary weeks with at least 4 days of diary data
5409/ 51/ White	Divigel® 0.5 g	No post-baseline diary data
8507/ 58/ White	Divigel® 0.5 g	No post-baseline diary data
8610/ 53/ White	Divigel® 0.5 g	No post-baseline diary data

Note: Patient ID 2947, 5409, 8507 and 8610 were recorded missing diary period records in the electronic efficacy data set DIARL.XPT.

Four hundred thirty-seven (88.3%) of the 495 treated patients completed the study. A total of 58 (11.7%) patients discontinued prematurely: 13 due to lack of efficacy, 12 for protocol violations, 12 chose to withdraw, nine due to AEs, nine were lost to follow-up, the Sponsor chose to withdraw two patients, and the investigator chose to withdraw one patient.

The overall completion/withdrawal was comparable between active and placebo groups. Discontinuations due to lack of efficacy were more common in the placebo and the 0.25 g and 0.5 g Divigel® dose groups than in the 1.0 g Divigel® dose group. Similarly, discontinuations due to voluntary withdrawal were more common in the placebo and the 0.25 g Divigel® dose group than in the 0.5 g and 1.0 g Divigel® dose group. Further dose response-related effects were noted for withdrawals due to AEs: seven patients withdrew due to AEs in the 1.0 g Divigel® dose group compared to one in the placebo, none in the 0.25 g, and one in the 0.5 g Divigel® dose groups, respectively.

The number of patients enrolled at each site was disproportionate and generally too small for most of the sites (<6 patients) to evaluate any site-related effects on patient disposition.

Table 2: (Sponsor's Table 10.1-1) summarizes patient disposition for randomized patients and reasons for withdrawal.

Table 2: Patient Disposition by Treatment Group – Randomized Sample

	USL-221			Placebo	Total
	1.0 g n=125	0.5 g n=123	0.25 g n=122	n=125	N=495
	Number of patients (%)				
Completed	111 (88.8%)	107 (86.0%)	108 (88.5%)	111 (88.8%)	437 (88.3%)
Discontinued	14 (11.2%)	16 (13.0%)	14 (11.5%)	14 (11.2%)	58 (11.7%)
Reason for withdrawal					
Lack of efficacy	0	5 (4.1%)	4 (3.3%)	4 (3.2%)	13 (2.6%)
Protocol violation	2 (1.6%)	4 (3.3%)	3 (2.5%)	3 (2.4%)	12 (2.4%)
Voluntary withdrawal	1 (0.8%)	1 (0.8%)	4 (3.3%)	6 (4.8%)	12 (2.4%)
Adverse event	7 (5.6%)	1 (0.8%)	0	1 (0.8%)	9 (1.8%)
Lost to follow up	2 (1.6%)	4 (3.3%)	3 (2.5%)	0	9 (1.8%)
Sponsor decision	1 (0.8%)	1 (0.8%)	0	0	2 (0.4%)
Physician decision	1 (0.8%)	0	0	0	1 (0.2%)
Analysis sample					
Intent-to-treat	124 (99.2%)	119 (96.7%)	121 (99.2%)	124 (99.2%)	488 (98.6%)
Per-protocol	101 (80.8%)	98 (79.7%)	97 (79.5%)	99 (79.2%)	395 (79.8%)
Safety	125 (100.0%)	123 (100.0%)	122 (100.0%)	125 (100.0%)	495 (100.0%)
[redacted]					(b) (4)

Note: Percentages are based on the number of randomized patients in each treatment group.

[redacted] (b) (4)

3.1.2.2 Patient characteristics

The patients participating in this study were primarily white postmenopausal women older than 50 years with an average of at least 50 moderate to severe hot flashes per week. In general, all four treatment groups were comparable in demographic and baseline characteristics, including medical history and baseline patient/disease characteristics. The average age of the overall population was 54.6 ± 6.78 years (range, 34.0-89.4 years). The proportion of patients 36 to 45 years of age was slightly lower in the Divigel® 0.5 g (6.5%) and 0.25 g (4.9%) treatment groups than in the Divigel® 1.0 g (11.2%) and placebo (11.2%) treatment groups. Although efforts were made by the Sponsor to select sites that would enroll patients to approximate the ethnic balance of the US and Canadian populations (such as the use of a Spanish consent form), most patients were white (86.5%) and not Hispanic or Latino (96.4%). The study population also included a small number of black (10.1%) patients, a smaller number of "Other," Asian, American Indian or Alaska Natives, or Native Hawaiian or other Pacific Islander race (3.4% combined), and a few Hispanic or Latino patients (3.6%). The demographic comparison of baseline failures and randomized patients are shown in Table 3 (Sponsor's post-text Table 6.1):

Table 3: Demographic Comparison of Baseline Failures and Randomized Patients

	Baseline Failure (N = 575)	Randomized (N = 495)
Age (years)		
n	575	495
Mean (SD)	54.18 (6.812)	54.65 (6.780)
Median	53.81	54.56
Min, Max	35.4, 80.3	34.0, 89.4
Age Categories (years)		
18 - 35	1 (0.2%)	4 (0.8%)
36 - 45	67 (11.7%)	42 (8.5%)
46 - 65	481 (83.7%)	427 (86.3%)
> =66	26 (4.5%)	22 (4.4%)
Ethnicity		
Hispanic or Latino	18 (3.1%)	18 (3.6%)
Not Hispanic or Latino	557 (96.9%)	477 (96.4%)
Race		
American Indian or Alaska Native	1 (0.2%)	2 (0.4%)
Asian	4 (0.7%)	6 (1.2%)
Black or African American	72 (12.5%)	50 (10.1%)
Native Hawaiian or Other Pacific Islander	2 (0.3%)	1 (0.2%)
White	486 (84.5%)	428 (86.5%)
Other	10 (1.7%)	8 (1.6%)

Note: Four patients (2345, 5414, 5701, and 8404) were randomized in error and are considered baseline failures. No drug was dispensed and no post-baseline data was collected. These four patients are excluded from the Randomized Sample for all analyses.

Demographic characteristics (age, ethnicity, and race) are summarized by treatment group in Table 4 (Sponsor's Table 11.2-1).

Table 4: Summary of demographics – Randomized sample

	Divigel®			Placebo	Total
	1.0 g n =125	**0.5 g n=123**	**0.25 g n=122**	**n=125**	**N=495**
Age (years)					
n	125	123	122	125	495
Mean	54.19	54.77	55.20	54.44	54.65
(SD)	(7.074)	(7.195)	(6.159)	(6.678)	(6.780)
Median	53.34	54.83	54.90	54.58	54.56
Min, Max	34.7, 70.2	34.0, 89.4	35.9, 73.0	34.4, 71.3	34.0, 89.4
Age group (years)					
18-35	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	4 (0.8%)
36-45	14 (11.2%)	8 (6.5%)	6 (4.9%)	14 (11.2%)	42 (8.5%)
46-65	106 (84.8%)	106 (86.2%)	110 (90.2%)	105 (84.0%)	427 (86.3%)
≥66	4 (3.2%)	8 (6.5%)	5 (4.1%)	5 (4.0%)	22 (4.4%)
Race, n (%)					
White	111 (88.8%)	108 (87.8%)	102 (83.6%)	107 (85.6%)	428 (86.5%)
Black or African American	11 (8.8%)	12 (9.8%)	13 (10.7%)	14 (11.2%)	50 (10.1%)
Other	0	1 (0.8%)	4 (3.3%)	3 (2.4%)	8 (1.6%)
Asian	2 (1.6%)	2 (1.6%)	2 (1.6%)	0	6 (1.2%)
American Indian/Alaska Native	0	0	1 (0.8%)	1 (0.8%)	2 (0.4%)
Native Hawaiian or Other Pacific Islander	1 (0.8%)	0	0	0	1 (0.2%)
Ethnicity, n (%)					
Not Hispanic or Latino	122 (97.6%)	118 (95.9%)	118 (96.7%)	119 (95.2%)	477 (96.4%)
Hispanic or Latino	3 (2.4%)	5 (4.1%)	4 (3.3%)	6 (4.8%)	18 (3.6%)

3.1.3 Sponsor's Statistical Analysis

3.1.3.1 Methods

Missing data: For all endpoints, if diary data were missing for a specific date in the baseline period, then that date was not included in calculations. Missing post-baseline diary data was carried forward from the preceding week diary**.** That is, for any missing post-baseline diary week (a week with fewer than four valid days), including weeks after a patient discontinued early from the study, the mean daily value of frequency or severity of MSVS was carried forward from the last preceding valid diary week.

Analyses: The primary efficacy analysis was based on the ITT population and the difference in change in daily frequency and severity of MSVS between Divigel® and placebo from baseline to week 4 and 12 was compared by the analysis of covariance (ANCOVA) including treatment group, pooled center, and baseline values as covariates. The number of MSVS was obtained from the weekly patient diaries.

The normality assumption was examined by using the Wilk-Shapiro test on the residuals from the ANCOVA model. For the primary and secondary efficacy endpoints, the normality assumption was not met for the ANCOVA model. Therefore, the van Elteren test, an extension of the Wilcoxon rank sum test, stratified by pooled center was used to evaluate the treatment comparisons between each active dose and placebo for that endpoint.

In addition, a model with treatment-by-pooled–center interaction as a class effect was constructed and the *p*-value for the Gail and Simon test for qualitative interaction was direction of treatment effects across pooled sites, which may indicate that patients at some pooled sites benefited from treatment while patients at other pooled sites did not. A quantitative interaction indicating variation in the magnitude but not the direction of treatment effects across pooled sites was not of interest and was not tested. The treatment by pooled-site interaction term was not significant at the 0.05 level; therefore, additional analyses were not required.

For categorical endpoints the Cochran-Mantel-Haenszel (CMH) test was used.

Patients who received any of the three different volumes of placebo (corresponding to the 0.25 g, 0.5 g, and 1.0 g active dose volumes) were grouped together as a placebo group to compare with each of the three active groups (Divigel® 0.25 g, 0.5 g, and 1.0 g) in all analyses. All analyses were based on patients in the defined population (Randomized, ITT, PP, VVA, or Safety) with non-missing values of the endpoint.

The Sponsor also performed a responder analysis to support the primary analysis based on the definition of responder as follows:

A responder is a patient who experiences at least a 50% reduction in the daily frequency of MSVS from baseline.

Level of Statistical Significance: All tests of hypotheses were performed at a 5% two-sided level of significance, unless otherwise specified. *P*-values were presented to three decimal places. Any *p*-value that was less than 0.001 was reported as <0.001, and the *p*-values that were greater than 0.999 were reported as >0.999.

With four co-primary endpoints (change in daily frequency of MSVS from baseline to week 4 and 12, change in daily severity of MSVS from baseline to week 4 and 12) and three active dose levels (Divigel 1.0 g, 0.5 g and 0.25 g), the type-I error rate was controlled by following a step-down test procedure. Starting with the highest dose, the treatment effect contrasts for four co-primary endpoints needed to be statistically significant at the testwise 0.05 level in order for the highest dose to be considered effective. If all four highest dose contrasts were significant, the four treatment effect contrasts for the next lower dose were evaluated at the 0.05 level. Again, if all four contrasts were statistically significant at the 0.05 level, then this dose was considered effective. The process was continued until a *p*-value equal to or greater than 0.05 was

observed on any one contrast within a dose level, or until all active doses versus placebo were evaluated.

3.1.3.2 Results

3.1.3.2.1 Primary analysis

3.1.3.2.1.1 Change in daily frequency of MSVS

Table 5 (Sponsor's Table 11.4-1) summarizes the change in daily frequency of MSVS by treatment group from baseline to weeks 4 and 12 using LOCF for the ITT population.

The Sponsor's analysis showed that each of the three USL-221(Divigel®) treatment groups demonstrated statistically significant reductions in median daily frequency of MSVS from baseline to week 12 when compared to placebo ($p<0.001$). The USL-221 1.0 g and 0.5 g treatment groups also demonstrated statistically significant reductions in median daily frequency of MSVS from baseline to week 4 when compared to placebo ($p\leq0.011$). While USL-221 0.25 g treatment group also demonstrated a greater reduction from baseline to week 4 in median daily frequency of MSVS (-5.00 episodes) when compared to placebo (-3.63 episodes), this difference did not reach statistical significance. Further analysis of the change in median daily frequency of MSVS in the USL-221 0.25 g treatment group showed that a statistically significant reduction from baseline compared to placebo was reached beginning at week 5 ($p=0.005$); statistically significant reductions compared to placebo were maintained at each time point through week 12 of treatment ($p\leq0.001$).

In general, a dose-response relationship was apparent for USL-221 in the reduction in median daily frequency of MSVS from baseline to weeks 4 and 12, with the 1.0 g treatment group showing the greatest response (-7.20 episodes at week 4 and -8.35 episodes at week 12) compared to the 0.5 g (-5.73 episodes at week 4 and -7.29 episodes at week 12) and 0.25 g (-5.00 episodes at week 4 and -6.88 episodes at week 12) treatment groups.

Table 5: Summary of Mean Daily Frequency of Moderate to Severe Vasomotor Symptoms at Baseline and Change from Baseline at Weeks 4 and 12 using LOCF - ITT Population

	USL-221			Placebo
	1.0 g n=124	0.5 g n=119	0.25 g n=121	n=124
Mean daily frequency of moderate to severe vasomotor symptoms				
Baseline				
n	124	119	121	124
Mean (SD)	10.69 (4.083)	10.86 (4.356)	12.11 (9.942)	10.79 (5.815)
Median	9.64	9.24	9.72	9.32
Week 4 change from baseline				
n	124	119	121	124
Mean (SD)	–7.63 (4.729)	–6.17 (5.232)	–5.66 (5.877)	–4.56 (6.420)
Median	–7.20	–5.73	–5.00	–3.63
p-value[1]	<0.001	0.011	0.132	-
Week 12 change from baseline				
n	124	119	121	124
Mean (SD)	–8.92 (4.860)	–7.48 (5.126)	–7.83 (8.486)	–5.27 (6.506)
Median	–8.35	–7.29	–6.88	–4.48
p-value[1]	<0.001	<0.001	<0.001	-

[1] Comparison significant if $p<0.05$; *p*-value from ANCOVA model of treatment group, pooled center, and baseline covariate. The assumption of normality was not met using the Wilk-Shapiro test. A van Elteren's test stratified by pooled center was used to evaluate treatment comparisons between each active dose and placebo.

Reviewer's comments:

1. The primary endpoints were defined as change in mean daily frequency of MSVS from baseline to week 4 and 12. The Sponsor's analysis was to test the difference in mean of these two primary endpoints between Divigel® groups and placebo. Since the normality assumption was not satisfied for the ANCOVA model, the van Elteren test was used. Therefore, the significant results can be only claimed on the difference in ***median*** *change in the mean daily frequency of MSVS between the Divigel® groups and placebo or claim on the reduction in median daily frequency of MSVS compared the Divigel® groups to placebo by using this reviewer's definition for the primary endpoints.*

2. *The weekly mean of change from baseline in mean daily frequency of MSVS using LOCF is graphically displayed for the ITT population by treatment group in Sponsor's Figure 11.4-3. Since the van Elteren test was used, plotting weekly mean change in daily frequency from baseline with p-value from van Elteren test is misleading. Therefore, it is not displayed in this report.*

3.1.3.2.1.2 Change in daily severity of MSVS

Table 6 (Sponsor's Table 11.4-3) summarizes the change in daily severity of MSVS by treatment group from baseline to week 4 and week 12 using LOCF for the ITT population.

Table 6: Summary of Mean Daily Severity of Moderate to Severe Vasomotor Symptoms at Baseline and Change from Baseline at Weeks 4 and 12 Using LOCF - ITT Population

	USL-221			Placebo
	1.0 g n=124	0.5 g n=119	0.25 g n=121	n=124
Mean daily severity of MSVS				
Baseline				
n	124	119	121	124
Mean[1] (SD)	2.52 (0.209)	2.52 (0.226)	2.53 (0.202)	2.53 (0.243)
Median	2.52	2.51	2.52	2.54
Week 4 change from baseline				
n	124	119	121	124
Mean[1] (SD)	−0.87 (0.961)	−0.65 (0.931)	−0.34 (0.704)	−0.25 (0.621)
Median	−0.47	−0.18	−0.07	−0.04
p-value[2]	<0.001	<0.001	0.283	-
Week 12 change from baseline				
n	124	119	121	124
Mean[1] (SD)	−1.39 (1.087)	-1.00 (1.085)	−0.84 (1.055)	−0.47 (0.863)
Median	−1.69	−0.56	−0.33	−0.13
p-value[2]	<0.001	0.002	0.021	-

[1] Mean values represent the severity score of moderate to severe vasomotor symptom [calculated as (2 x moderate symptoms + 3 x severe symptoms)/total number of moderate and severe symptoms].

[2] Comparison significant if $p<0.05$; *p*-value from ANCOVA model of treatment group, pooled center, and baseline covariate. The assumption of normality was not met using the Wilk-Shapiro test. A van Elteren's test stratified by pooled center was used to evaluate treatment comparisons between each active dose and placebo.

All three doses of Divigel® treatment groups demonstrated statistically significant reductions in median daily severity of MSVS from baseline to week 12 when compared to placebo ($p\leq0.021$). The Divigel® 1.0 g and 0.5 g treatment groups also demonstrated statistically significant reductions in median daily severity of MSVS from baseline to week 4 when compared to placebo ($p<0.001$). The Divigel® 0.25 g treatment group had a greater reduction from baseline to week 4 in median daily severity of MSVS (-0.07) when compared to placebo (-0.04), this difference did not reach statistical significance at this time point. Further analysis of the change in median daily severity of MSVS in the Divigel® 0.25 g treatment group showed that a statistically significant reduction from baseline compared to placebo was reached beginning at week 5 ($p=0.038$) and was maintained at weeks 7 through 12 of treatment ($p\leq0.022$).

In general, a dose-response relationship was apparent for Divigel® in the reduction in median daily severity of MSVS from baseline to weeks 4 and 12, with the 1.0 g treatment

group showing the greatest response (-0.41 at week 4 and -1.69 at week 12), compared to the 0.5 g (-0.18 at week 4 and -0.56 at week 12) and the 0.25 g (-0.04 at week 4 and -0.13 at week 12) treatment groups.

3.1.3.2.2 Responder Analysis

A responder was defined as a patient who experienced at least a 50% reduction in daily frequency of MSVS from baseline to weeks 4, 8, or 12. Table 7 (Sponsor's Table 11.4-7) summarizes the number of responders using LOCF for the ITT sample by week and treatment group.

Table 7: Summary of Responders at Weeks 4, 8, and 12 Using LOCF – ITT Population

	USL-221			Placebo
	1.0 g n=124	0.5 g n=119	0.25 g n=121	n=124
	Number of patients (%)			
Week 4				
Responder	98 (79.0%)	71 (59.7%)	64 (52.9%)	51 (41.1%)
Non-responder	26 (21.0%)	48 (40.3%)	57 (47.1%)	73 (58.9%)
p-value[1]	<0.001	0.016	0.059	-
Week 8				
Responder	111 (89.5%)	87 (73.1%)	82 (67.8%)	60 (48.4%)
Non-responder	13 (10.5%)	32 (26.9%)	39 (32.2%)	64 (51.6%)
p-value[1]	<0.001	0.001	0.002	-
Week 12				
Responder	111 (89.5%)	86 (72.3%)	82 (67.8%)	60 (48.4%)
Non-responder	13 (10.5%)	33 (27.7%)	39 (32.2 %)	64 (51.6%)
p-value[1]	<0.001	0.003	0.014	-

[1] Comparison significant if $p<0.05$; *p*-value from CMH test adjusting for pooled center.

Table 7 shows that for each of the three Divigel® treatment groups, the percentage of patients who were considered responders was statistically significantly greater when compared to placebo at weeks 8 ($p\leq0.002$) and 12 ($p\leq0.014$). The Divigel® 1.0 g and 0.5 g treatment groups also demonstrated statistically significantly greater percentages of responders at week 4 when compared to placebo ($p\leq0.016$). While the Divigel® 0.25 g treatment group demonstrated a greater percentage of responders at week 4 (52.9%) when compared to placebo (41.1%), this difference did not reach statistical significance at this time point ($p=0.059$).

3.1.4 Reviewer's Analysis

3.1.4.1 Methods

The van Elteren test with stratified by pooled center was used in the reviewer's analysis for the four co-primary endpoints – the change in daily frequency of MSVS from baseline to week 4 and week 12, and the change in daily severity of MSVS from baseline to week 4 and 12. Since the van Elteren test is a rank based non-parametric test, the median change from baseline in daily frequency of MSVS and the median change from baseline in daily severity of MSVS in Divigel groups were compared to that of placebo. These tests were done for every week from week 1 to week 12.

A responder analysis was also conducted by the reviewer. Two types of responders related to co-primary endpoints were considered in the reviewer's analysis. They are:

Responder to the daily frequency of MSVS in a week:

A patient who experienced at least 50% reduction in daily frequency of MSVS from baseline in a week.

Responder to the daily severity of MSVS in a week:

A patient who experienced at least 50% reduction in daily severity of MSVS from baseline in a week.

For support the primary analysis, the efficacy assessment was based on the significance results from responder rates in week 4 and week 12 for both daily frequency of MSVS and daily severity of MSVS. The Cochran-Mantel-Haenszel (CMH) test with stratified pooled centers was used for the responder analysis.

The step-down procedure proposed by the Sponsor for the statistical significance of an endpoint at 0.05 level was used in both the van Elteren test and the CMH test.

3.1.4.2 Results

3.1.4.2.1 Primary analysis

The study results show that:

1. Each of the three Divigel® treatment groups, 1.0 g, 0.5 g and 0.25 g, demonstrated statistically significant reductions in median daily frequency of MSVS from baseline to week 12 when compared to placebo ($p \leq 0.001$). The Divigel® 1.0 g and 0.5 g treatment groups also demonstrated statistically

significant reductions in median daily frequency of MSVS from baseline to week 4 when compared to placebo ($p \leq 0.011$).

2. Each of the three Divigel® treatment groups also demonstrated statistically significant reductions in median daily severity of MSVS from baseline to week 12 when compared to placebo ($p \leq 0.021$). Divigel® 1.0 g and 0.5 g treatment groups also demonstrated statistically significant reductions in median of the mean daily severity of MSVS from baseline to week 4 when compared to placebo ($p < 0.001$).

3. For Divigel® 1.0 g and 0.5 g treatment groups, these statistically significant differences from placebo were maintained at each subsequent time point for the duration of treatment through week 12.

4. The Divigel® dose regimen 0.25 g daily was ineffective in demonstrating changes in median daily frequency or severity of MSVS from baseline to week 4 in the primary analysis. The statistically significant improvements from baseline in both median daily frequency and median daily severity of MSVS compared to placebo were observed in the 0.25 g treatment group ($p=0.005$ and $p=0.038$ respectively) at week 5. However, the significant differences from placebo for change from baseline in median daily severity in this treatment group did not maintain the significance at week 6 ($p=0.208$).

(See Tables 8 and 9, and Figures 1 and 2).

Table 8: Results from the van Elteren test for Median Change in Daily Frequency of MSVS from Baseline by Week Using LOCF, ITT Population

	Divigel®1.0 g N=124			Divigel® 0.5 g N=119			Divigel® 0.25 g N=121			Placebo N=124	
Week	Median	Change from Baseline		Median	Change from Baseline		Median	Change from Baseline		Median	Change from Baseline
-1	9.64			9.24			9.72			9.32	
1	7.57	-2.34		7.64	-1.75		8.43	-1.63		7.29	-2.43
2	4.71	-4.68	**	6.43	-4.00		7.07	-3.16		6.57	-3.30
3	2.50	-6.60	***	4.71	-4.71		5.57	-4.29		5.93	-3.63
4	1.93	-7.20	***	3.71	-5.73	*	4.86	-5.00		5.64	-3.63
5	1.36	-7.34	***	3.43	-6.63	**	3.86	-5.71	**	5.57	-4.05
6	1.14	-7.61	***	2.86	-6.79	***	3.86	-5.71	***	5.66	-4.06
7	1.02	-7.71	***	2.29	-7.14	***	3.29	-6.62	***	5.36	-4.37
8	0.86	-7.82	***	2.29	-7.29	***	3.43	-6.33	***	5.36	-4.75
9	0.64	-7.88	***	1.86	-7.14	***	3.14	-6.71	***	5.36	-4.56
10	0.36	-8.15	***	1.86	-7.00	***	3.00	-6.71	***	5.43	-4.45
11	0.43	-8.29	***	1.57	-7.18	***	2.86	-6.88	***	5.21	-4.57
12	0.43	-8.35	***	1.57	-7.29	***	3.00	-6.88	***	4.93	-4.48

Note: The van Elteren's test stratified by pooled center was used to evaluate treatment comparisons between each active dose and placebo. Week -1 denotes baseline. ***, **, * denote statistical significant compared to placebo at the 0.001, 0.01 and 0.05 levels, respectively.

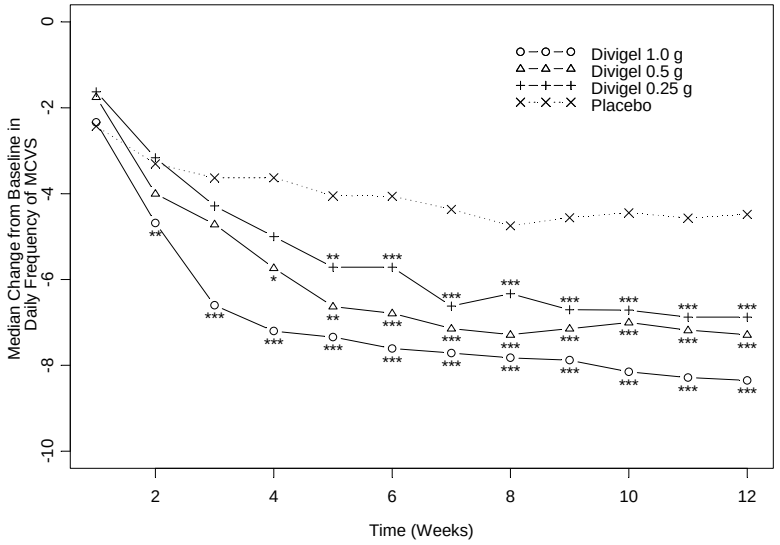

Figure 1: Median Change From Baseline in Daily Frequency of MSVS by Week Using LOCF − ITT Population

Note: ***: $p \leq 0.001$, **: $p \leq 0.01$, *: $p \leq 0.05$

Table 9: Results From the van Elteren Test for Median Change in Daily Severity of MSVS From Baseline by Week Using LOCF, ITT Population

	Divigel® 1.0 g N=124			Divigel® 0.5 g N=119			Divigel® 0.25 g N=121			Placebo N=124	
Week	Median	Change from Baseline		Median	Change from Baseline		Median	Change from Baseline		Median	Change from Baseline
-1	2.52			2.51			2.52			2.54	
1	2.46	-0.04		2.46	-0.01		2.51	-0.01		2.49	-0.01
2	2.39	-0.12	*	2.44	-0.04	*	2.47	-0.03		2.44	-0.04
3	2.12	-0.27	***	2.38	-0.10	**	2.41	-0.08		2.44	-0.04
4	2.02	-0.47	***	2.27	-0.18	***	2.39	-0.07		2.45	-0.04
5	1.78	-0.67	***	2.26	-0.29	***	2.31	-0.16	*	2.44	-0.04
6	1.71	-0.76	***	2.14	-0.39	***	2.31	-0.13		2.45	-0.05
7	1.38	-1.06	***	2.00	-0.46	***	2.25	-0.24	***	2.43	-0.06
8	1.14	-1.19	***	2.00	-0.56	***	2.21	-0.26	**	2.43	-0.07
9	0.89	-1.60	***	2.02	-0.47	***	2.19	-0.31	***	2.40	-0.07
10	0.57	-1.78	***	2.00	-0.57	***	2.19	-0.27	*	2.43	-0.08
11	0.79	-1.78	***	2.00	-0.56	***	2.12	-0.33	*	2.43	-0.07
12	0.86	-1.69	***	2.00	-0.56	**	2.11	-0.33	*	2.42	-0.13

Note: The van Elteren's test stratified by pooled center was used to evaluate treatment comparisons between each active dose and placebo. Week -1 denotes baseline. ***, **, * denote statistical significant compared to placebo at the 0.001, 0.01 and 0.05 levels, respectively.

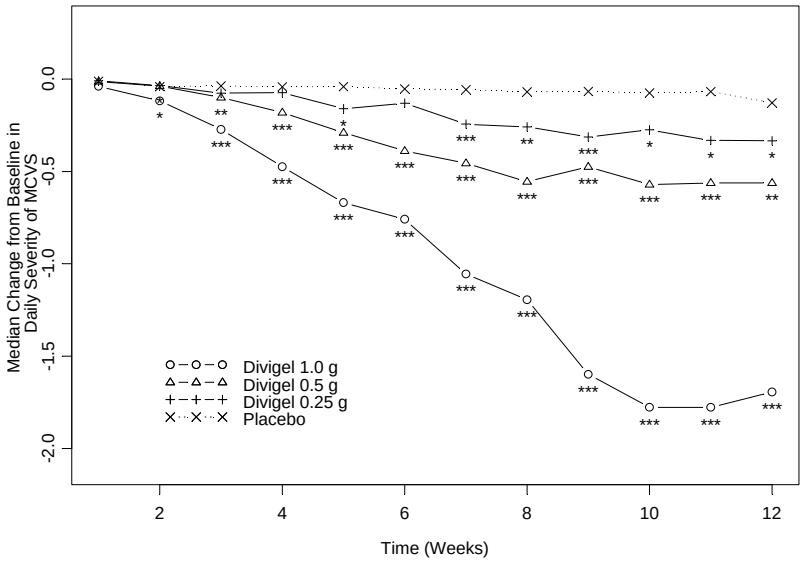

Figure 2: Median Change From Baseline in Daily Severity of MSVS by Week Using LOCF − ITT Population

Note: ***: $p \leq 0.001$, **: $p \leq 0.01$, *: $p \leq 0.05$

3.1.4.2.2 Responder Analysis

Table 10 summarizes the results of responder analysis for both co-primary endpoints LOCF for missing data. The analysis showed that Divigel® 1.0 g and 0.50 g doses consistently demonstrated statistically significant reductions in regarding to both co-primary endpoints as early as week 4. The Divigel® 0.25 g dose, however, did not demonstrate significant reductions until week 5 for frequency and until week 7 for severity. The p-values from the CMH test with stratified by pooled center at week 4 are 0.147 and 0.524 for frequency and severity, respectively. Figures 3 and 4 show the responder rates versus week with marks for the p-values from CMH test.

Table 10: Summary of Responder Rates for Frequency or Severity of MSVS by Week Using LOCF (Study P04-001), ITT Population

	Divigel® 1.0 g N=124				Divigel® 0.5 g N=119				Divigel® 0.25 g N=121				Placebo N=124	
Week	Frequency		Severity		Frequency		Severity		Frequency		Severity		Frequency	Severity
1	0.22		0.02		0.19		0.03		0.13		0.03		0.24	0.06
2	0.51	*	0.08		0.39		0.10		0.26		0.04		0.38	0.08
3	0.71	***	0.23	***	0.53		0.16	*	0.46		0.07		0.41	0.06
4	0.79	***	0.33	***	0.60	*	0.25	***	0.53		0.10		0.41	0.10
5	0.82	***	0.41	***	0.62	**	0.29	***	0.60	*	0.17		0.41	0.09
6	0.86	***	0.42	***	0.69	***	0.31	***	0.61	**	0.19		0.44	0.10
7	0.85	***	0.48	***	0.72	***	0.32	***	0.69	**	0.24	*	0.41	0.12
8	0.90	***	0.49	***	0.73	***	0.33	**	0.68	**	0.23	*	0.48	0.15
9	0.87	***	0.57	***	0.71	***	0.34	***	0.68	***	0.27	**	0.48	0.13
10	0.88	***	0.56	***	0.73	***	0.39	***	0.69	***	0.31	**	0.49	0.13
11	0.87	***	0.56	***	0.70	***	0.39	***	0.69	***	0.30	**	0.48	0.15
12	0.90	***	0.55	***	0.72	***	0.39	**	0.68	**	0.31	*	0.48	0.18

Note: The Cochran-Mantel-Haenszel test with stratified by pooled center was used to evaluate treatment comparisons between active dose and placebo. ***, **, * Statistical significant compared to placebo at the 0.001, 0.01 and 0.05 levels, respectively

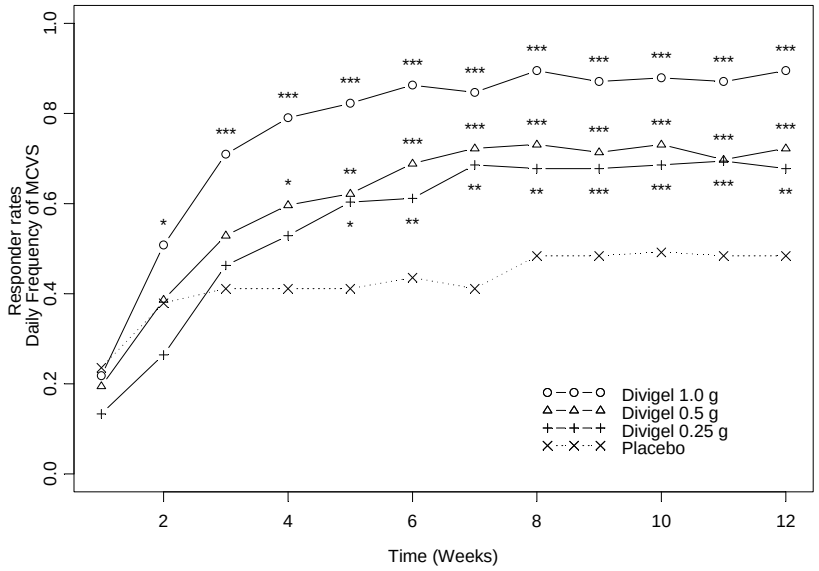

Figure 3: Responder Rates of Daily Frequency of MSVS by Week Using LOCF − ITT Population

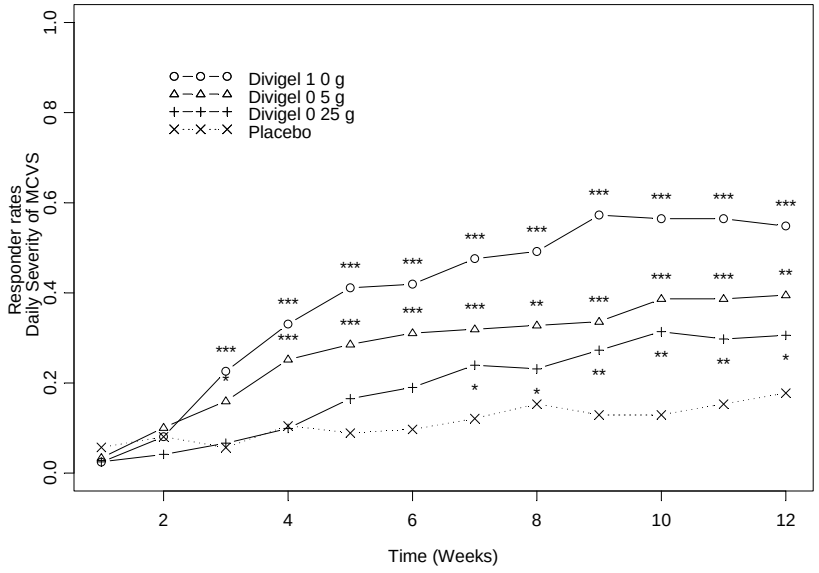

Figure 4: Responder Rates of Daily Severity of MSVS by Week Using LOCF − ITT Population

Notice that a responder to severity of MSVS must be a responder to frequency of MSVS. Table 11 lists several 2×2 tables for summarizing responder rates from responders to both frequency and severity of MSVS (the same as responders to severity of MSVS) in either week 4 or week 12 by treatments.

Table 11: Comparison in responder rates (%) from responders to both frequency and severity of MSVS

Week	Placebo		
4\12	R	N	Total
R	8.1	2.4	10.5
N	9.7	79.8	89.5
Total	17.8	82.2	100

Week	Divigel® 0.25 g		
4\12	R	N	Total
R	9.2	0.8	10.0
N	21.7	68.3	90.0
Total	30.9	69.1	100

	Divigel® 0.5 g		
4\12	R	N	Total
R	20.2	5.0	25.2
N	19.3	55.5	74.8
Total	39.5	60.5	100

Week	Divigel® 1.0 g		
4\12	R	N	Total
R	30.7	2.4	33.1
N	24.2	42.7	66.9
Total	54.9	45.1	100

Note: R: Represents responder; N: Non-responder.

It can be seen from Table 11 that there were small percentage of patients in each treatment group who were responders at week 4 but not at week 12. These rates are 2.4%, 5.0% and 0.8% for Divigel® 1.0 g, 0.5 g and 0.25 g respectively. The percentages of responders at week 12 but not at week 4 were 24.2%, 19.3% and 21.7% for Divigel® 1.0 g, 0.5 g and 0.25 g respectively. There are quite large percentages of the patients who were not responders at week 12 (45.1%, 60.5% and 69% for Divigel® 1.0 g, 0.5 g and 0.25 g respectively) although the differences in responder rates between Divigel® treatments and placebo are statistically significant at week 12. Clearly there was a dose response to the Divigel® treatments.

It also can also be seen that 17.8% of responders at week 12 in placebo group. Given patients in placebo group who were responders at week 12, 45.5% (8.1%/17.8%) of them were also responders at week 4.

The responders at both week 4 and 12 for Divigel® 0.25 g was 9.2%. Comparing with placebo group, Divigel® 0.25 g failed to demonstrate statistical significance in increasing responder rate.

3.2 Evaluation of Safety

There was no clinically significant difference between treatment groups in the number of subjects who completed Study P04-001 or in the reasons for discontinuation. No deaths

occurred during or following the conduct of Phase 3 Study P04-001 that used the to-be-marketed Divigel® formulation (USL 221).

Detailed safety assessment can be found in the Clinical Reviewer's report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Gender

All participants are postmenopausal women.

4.1.2 Race

Despite predominately white patient population (white 85% vs. non-white 14%), the efficacy results trended in the same direction. , Overall, Divigel® showed an improvement in the frequency and severity of MSVS in both the white and nonwhite populations. Due to disproportionate number of subjects, a meaningful comparison between the two subgroups could not be made.

4.1.3 Age

The average age of the overall population was 54.6 ± 6.78 years (range, 34.0-89.4 years). The proportion of patients 36 to 45 years of age was slightly lower in the Divigel® 0.5 g (6.5%) and 0.25 g (4.9%) treatment groups than in the Divigel® 1.0 g (11.2%) and placebo (11.2%) treatment groups.

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A statistical analysis plan (SAP) detailed the planned analyses of the protocol and was finalized on 01 September 2005 by the Sponsor. The SAP was amended on 21 November 2005 prior to unblinding and data lock to 1) establish data handling rules for duplicate and blank diary entries; 2) further define missing diary data in the baseline and post-

baseline periods; 3) clarify the application of the LOCF approach; 4) further define the analysis for pooled center interaction; 5) redefine the criteria for the (b) (4), and 6) redefine the analysis of covariance (ANCOVA) model used for the efficacy analysis.

During the review of this application, the reviewer noted the following issues:

5.1.1 Data entry and Source data (patient diary data) problems

The Sponsor's primary dataset for analysis was set as DIARL.xpt. It was reported that subjects: ID 2947, ID 5409, ID 8507 and ID 8610 were excluded from ITT population due to no post-baseline diary data. It was noted that missing values were recorded for the variable DIARP in the efficacy data set DIARL.xpt for those patients.

DIARP was the column in the primary dataset that represented the weeks as recorded on a daily basis during either the screening period for baseline or during treatment period. The entries for DIARP were recorded using -1 or positive integers respectively for each screening or treatment week. The dataset, without seeing the original patient diary, was based on the missing data records for DIARP. Therefore, one would not be able to identify that the records of daily frequencies for MSVS of those patients were from screening period or treatment periods. The actual diaries were specified separately as being used during a screening period or a treatment period.

The reviewer noted that if a patient recorded her frequencies for MSVS, it would be impossible to have missing value for variable DIARP. Therefore, the action on excluding those patients from the ITT population is questionable.

Both the statistical reviewer and clinical reviewers examined patient diaries. It was clear that the format of the diaries was not optimal. The source diary had no patient ID on each page of the diaries, and there was no page numbers on the diaries. In addition, the reviewers' noted that some changes were made on a diary including dates, different hand writings, and other changes including crossed out study week numbers. Some of these changes were without any initials next to the changes, or without a reason as to why the changes were made.

The Sponsor's protocol allowed subjects to have two different diary records for the same day on the day of a visit. This caused some patients to have records that appeared to show subjects applying the medication twice per day, or having an initial diary entry that was blank for vasomotor symptoms. The Sponsor's revised SAP allowed subjects to add these diary entries together, but it is unclear whether in these cases the blank information should have been counted as zero.

In this reviewer's opinion, allowing subjects to start a new diary on the visit day appeared to have caused confusion in some subjects that turned their diaries in to the investigator. This reviewer has concerns that by adding this information, this was not the most conservative way to handle this visit day information.

5.1.2 Definition of ITT population

The Sponsor excluded patients ID 2931 in Divigel® 1.0 g group, ID 4209 in placebo group, ID 4213 in Divigel® 0.5 g group from ITT population, because these patients did not have at least one valid diary period post baseline. A valid diary period was defined as a week with at least four days of diary data recorded. This definition of ITT population is different from the conventional definition used in clinical trials. The revised ITT definition was defined in the Sponsor's revised SAP (which provided additional details of the planned analyses of Study P04-001). This SAP was finalized on 01 September 2005 and amended on 21 November 2005.

Reviewer's comment: In this reviewer's opinion, the definition of the ITT population was not optimal. However, since only three patients were excluded from the ITT population for this reason, and those patients belonged to three different treatment groups (including placebo group), this reviewer does not believe that the efficacy results were significantly affected by this ITT population definition for this study.

5.1.3 Primary endpoints

The primary endpoints for VMS indication were the changes in the mean daily frequency and severity of moderate to severe vasomotor symptoms from baseline to week 4 and 12 The mean in the definition of the primary endpoints is referred to within subject average daily frequency (or severity) in a week for a subject. For avoiding the confusion with population mean which is the parameter of interest in the study, in this reviewer's opinion, the "mean" should be omitted in the definition of the primary endpoints.

5.1.4 LOCF Method

The four co-primary endpoints used to determine efficacy of Divigel® for MSVS indication were the change from baseline to 4 week and from baseline to week 12 in mean daily frequency and severity of MSVS using the last observation carried forward (LOCF) method in patients receiving one of three dose amounts of Divigel® versus those receiving placebo. Symptoms were recorded daily by the patient in a self-evaluation daily diary.

The Sponsor defined the LOCF method as follows: For any invalid post-baseline diary week (a week with fewer than four valid days), including weeks after a patient discontinued early from the study, the mean daily value of frequency or severity of MSVS was carried forward from the last preceding valid diary week.

Reviewer's comments: The LOCF defined by the Sponsor threw away data information in a diary week with less than 4 valid days. In this reviewer's opinion, if a patient had less than 4 valid days in a week, the co-primary endpoints for the week should be calculated using observations from the last 7 valid dairy days.

5.1.5 Blanks in Vasomotor Symptom (VS) Diary

The Sponsor stated that it was recognized that patients used different recording styles to record the daily vasomotor symptom counts. Some subjects would record values only when they experienced a VS in that specific category of severity (mild, moderate, severe) and might have left a VS field(s) blank when they did not experience VS of the specific severity category. Therefore, the following rule was used to account for the multiple recording styles in the diary data:

- If the date of collection, the gel application site, and all of the (b) (4) symptom fields were completed on a specific day, then it was assumed that the patient actively completed the diary for that day. Under this assumption, a value of zero (0) was imputed for any blank mild, moderate, or severe vasomotor symptom field(s) on that diary day.

The Sponsor also identified that a small number of patients recorded baseline VS severity data for only moderate or only severe symptoms and left the other VS severity records blank throughout the baseline period. To allow inclusion of these patients in the primary analysis, blank severity values were assigned zero (0) only in the situation where the patient had consistently completed the baseline period diary in this manner for the entire length of the baseline period.

Reviewer's comment: The Sponsor did not use most conservative way to account for blank diary entries. The most conservative way would have been to assign a zero to each blank in the baseline period and assigning the last preceding observation to the blanks in the post-baseline period for Divigel® group, and do the opposite for the placebo group.

Note: Imputation for blanks was not applied in the primary analysis.

5.1.6 Responder Analysis

In the responder analysis, the Sponsor defined a responder as a patient who experiences at least a 50% reduction in the daily frequency of MSVS from baseline.

Reviewer's comments: For MSVS indication, there are four co-primary endpoints, change in daily frequency of MSVS from baseline to week 4 and baseline to week 12 and change in daily severity of MSVS from baseline to week 4 and baseline to week 12. Therefore, the responder analysis should consider not only patients who experienced at least 50% reduction in daily frequency of MSVS but also those who experienced at least

50% reduction in daily severity. It was found that responders to reduction of the daily severity of MSVS from baseline were a subset of the responders to reduction of the daily frequency. In other words, some patients experienced at least 50% reduction in the daily frequency of MSVS, but not in the daily severity.

5.1.7 Dose titration scheme

The Sponsor intended to claim that Divigel® 0.25 g could be used in titrating women to a lower dose as menopause progresses. However, the Sponsor did not include a treatment group for a titration scheme in Study P04-001. Therefore, the efficacy and safety of a "step-down" treatment regime from a higher to lower dose could not be evaluated.

(b) (4)

5.2 Conclusions and Recommendations

Despite the suboptimal study conduct with regards to diary data, it appeared the efficacy data was not compromised to affect the conclusion.

In conclusion, the study demonstrated the efficacy for both the Divigel® 1.0 g and 0.5 g doses as early as week 4, and maintained through week 12. However, Divigel® 0.25 g dose did not demonstrate reduction in frequency and severity of moderate to severe vasomotor symptoms until week 5 and 7, respectively.

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Screening of New NDA for Statistical Filing
Division of Biometrics 3

NDA #: 22-038

Applicant: Upsher-Smith Laboratories, Inc.

Trade/Generic Name: Divigel, 0.25 mg, 0.5 mg, 1 mg (USL-221, Estradiol Gel, 0.1%)

Indication: Treatment of Moderate to Severe Vasomotor Symptoms (VMS) [redacted] (b) (4) Associated with the Menopause

Date of Submission: May 5, 2006

Filing Date: July 3, 2006

User Fee Goal Date: March 4, 2007

Project Manager: Mr. George Lyght (HFD-580)

Medical Reviewer: Bruce Patsner, M.D., J.D. (HFD-580)

Comments: The applicant is seeking an approval of their new drug, Divigel at dosages of 0.25 mg, 0.5 mg, and 1 mg, for the indication of "treatment of moderate to severe vasomotor symptoms (VMS) [redacted] (b) (4) associated with the menopause". This submission contains one Phase 3, placebo-controlled, randomized, double-blind, multicenter study (study # P04-001), to demonstrate the efficacy of 12 weeks of treatment with USL-221 on moderate to severe vasomotor symptoms [redacted] (b) (4) in postmenopausal patients, which will be the focus of the statistical review. This NDA can be filed.

A total of 488 subjects were evaluated for efficacy in the study # P04-001. Subjects were randomized to either one of the three dosages of Divigel or Placebo in a ratio of 1:1:1:1.

Objectives: The primary objective was to compare the change from baseline in mean daily frequency and severity of moderate to severe vasomotor symptoms (MSVS) at weeks 4 and 12 between USL-221 and placebo. [redacted] (b) (4)

Methodology: This was a randomized, parallel, placebo-controlled, double-blind, multicenter study in postmenopausal women with MSVS. Patients received treatment with USL-221 (Estradiol Gel, 0.1%) or placebo for 12 weeks. [redacted] (b) (4) This study consisted of a screening period, four study visits (Visits 2-5) for patients without an intact uterus, and five study visits (Visit 2-6) for patients with a uterus. For patients who required a washout from current hormone therapy, the screening period included a 4-week to 6-month washout period depending on the hormone therapy being discontinued. All patients with an intact uterus had a pretreatment endometrial biopsy attempted. If the pre-treatment biopsy results indicated "no tissue" or "tissue insufficient for diagnosis," then a transvaginal ultrasound (TVU) was used to determine the patient's eligibility for the study. Prior to randomization, patients completed the symptom diary for at least 12 days, which the screening evaluations were randomized to one of the following four treatment groups: 0.25 g, 0.5 g, 1.0 g USL-221, or matching placebo gel. All patients applied the study drug topically to the thigh once daily, alternating between the left and right thigh daily, for 12 weeks. Vasomotor symptoms [redacted] (b) (4) were recorded daily by the patient in a self-evaluation diary along with date, time, and site of study drug application. At study Visits 2, 3, and 4, the patient would receive a new diary and study medication and at study Visits 3, 4, and 5, the patient would turn in her diary and study medication. At completion of study treatment, patients with an intact uterus who received at least six weeks of study drug therapy received oral medroxyprogesterone once daily for 14 days followed by a TVU.

The primary efficacy assessments are MSVS, with the following as co-primary endpoints (measured by patient diary):

• Change in mean daily frequency of MSVS from baseline to week 4 and baseline to week 12; and

• Change in mean daily severity of MSVS from baseline to week 4 and baseline to week 12.

The primary efficacy analyses in the ITT population compared the change in mean daily frequency and severity of MSVS from baseline to week 4 and to week 12 using the LOCF approach for invalid weeks. These parameters were analyzed by an analysis of covariance (ANCOVA) including treatment group, pooled center, and baseline values as covariates. The number and severity of symptoms were obtained from the weekly patient diaries.

Based on the Sponsors' results, each of the three USL-221 treatment groups demonstrated statistically significant reductions in the mean daily frequency of MSVS from baseline to week 12 when compared to placebo ($p<0.001$). The USL-221 1.0 g and 0.5 g treatment groups also demonstrated statistically significant reductions in the mean daily frequency of MSVS from baseline to week 4 when compared to placebo ($p=0.011$).

The sponsor has provided this submission in both paper as well as electronic format. The electronic submission is located at: **\\Cdsesub1\N22038\N_000\2006-05-01**

Checklist for Fileability	Remarks (NA if not applicable)
Indexes 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	Review Issue
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	OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	NA

Reviewer: S. Farr

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