CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-323/S-021

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Addendum

NDA: 20-323/S-021
Trade Name: Vivelle® (Estradiol Transdermal System)
Sponsor: Novartis Pharmaceuticals Corporation.

This addendum pertains to the analysis of severity of hot flushes in study 036. Table B shows the mean change in severity of hot flushes/24 hour reported in the last week of each treatment cycle.

Table B
Mean Change (SD) from Baseline in Mean Overall Severity of Hot Flushes/24 hour in the Last Week of Cycle 1, 2, 3.

Treatment Group	Week 4 (Cycle 1)		Week 8 (Cycle 8)		Week 12 (Cycle 3)	
	n	Change(SD)	n	Change (SD)	n	Change (SD)
Vivelle 0.0375 mg	128	-1.32(.87)	129	-1.63 (.94)	124	-1.78 (.92)
Placebo	125	-0.70 (.75)	120	-0.88 (.85)	118	-0.94 (.88)
P-value *vs* Placebo		<0.05		<0.05		<0.05

The mean change from baseline in overall severity was larger for Vivelle patients than placebo patients. Our analysis shows that Vivelle 0.0375mg dose was statistically significantly better to placebo in reducing the mean severity of hot flushes/24 hour. The reduction in severity was maintained through week 8 and 12. Results from our analysis confirms sponsor's conclusion that low (0.0375mg) dose of vivelle was efficacious in reducing severity of hot flushes.

/S/ 2/24/00

Mahboob Sobhan, Ph.D.
Statistical Reviewer, HFD-715

Statistical Review and Evaluation
Addendum

NDA: 20-323/S-021
Trade Name: Vivelle® (Estradiol Transdermal System)
Sponsor: Novartis Pharmaceuticals Corporation.

As per Division's decision, the efficacy results were reanalyzed for the last week of cycle 1, 2, and 3 (week 4, 8, 12) as opposed to efficacy results for the last two weeks of cycle 1, 2, and 3 as presented in our earlier review. The results are shown in Table A. The Vivelle 0.0375mg dose was statistically significantly better to placebo in reducing the mean daily vasomotor symptoms at week 4 and maintained through week 8 and 12. The sponsor agreed to include a graphical presentation of the finding in the label.

Table A
Mean Change (SD) from Baseline in Mean Daily Hot Flushes/24 hour in a 12-week Trial

Treatment Group	Week 4		Week 8		Week 12	
	n	Change(SD)	n	Change (SD)	n	Change (SD)
Vivelle 0.0375 mg	130	-8.4 (5.7)	129	-9.4 (5.6)	126	-9.8 (6.0)
Placebo	125	-4.9 (4.8)	120	-5.8 (5.0)	118	-6.6 (5.3)
P-value *vs* Placebo		<0.05		<0.05		<0.05

/S/ 2/16/00

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STATISTICAL REVIEW AND EVALUATION

NDA:	20-323/S-021
Priority Classification:	1S
Trade Name:	Vivelle® (Estradiol Transdermal System)
Sponsor:	Novartis Pharmaceuticals Corporation.
Indications:	Vivelle® is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulval and vaginal atrophy; treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
Medical Officer:	Phill Price, M.D., HFD-580
Project Manager:	Diane Moore, HFD-580
Submission Date:	05/03/99

I. INTRODUCTION

I.1. Background

The sponsor, Novartis Pharmaceuticals, has submitted this supplemental application as a Phase IV commitment to FDA to revise the restrictive language in the dosage and administration section of the labeling that states that some women taking the 0.035 mg/day dosage of Vivelle® may experience a delayed onset of efficacy.

In the original submission, the efficacy of Vivelle was studied in two trials (study 1003-A and study 1003-B) involving dosages ranging from 0.035mg/day to 0.10mg/day compared to placebo. In these studies, the effectiveness of the low dose (0.035mg/day) was demonstrated only in study 1003-B but not in study 1003-A. In trial 1003-A, the low dose of Vivelle was not statistically significantly better than placebo in reducing the number of hot flushes in the last two weeks of cycle 1. In order to support that the low dose of Vivelle is also effective in the first treatment cycle, the sponsor conducted another Phase IV trial (study 036). This supplement included the safety and efficacy results from this trial conducted in a patient population similar to the post-menopausal women studied in the approved NDA. In addition, the sponsor also included the results of a re-analysis of data from study 1003-A.

This review will focus on the consistency of the efficacy results from this new Phase IV trial (study 036) compared to the results reported in the original NDA and the appropriateness of the *post hoc* re-analysis of data from the original NDA.

I.2. Review Issues

During the team discussions, the clinical/statistical team raised the following two issues:

> (1) Whether the evidence shown in support of the efficacy of 0.035 mg/day dose of Vivelle were consistent using both intent-to-treat and acceptable patient population in the Phase IV study (036) and,
>
> (2) Whether a re-analysis (using only patients with low dose of Vivelle and placebo) of study (1003-A) submitted in the original NDA was appropriate and concludes anything different from previous analyses?

With respect to (1), the sponsor's submission lacked the results using intent-to-treat patients, as planned in the protocol. Therefore, the clinical/statistical team requested the sponsor either to provide the results of their analysis or guide FDA to perform the appropriate analysis. With respect to (2), the team decided to review the results of the sponsor's re-analysis of data from study 1003-A. The sponsor's original analysis failed to demonstrate the efficacy at the end of week 3 and week 4, which was also confirmed by FDA analysis. This review will verify the strength of this *post hoc* analysis compared to the earlier analysis. It was also decided that the results of the current study (036) would be instrumental in making the proposed labeling change recommendations.

II. Phase IV Study

II.1. Description of Study 036

Study 036 was a randomized, double-blind, parallel group, 12-week multicenter study designed to compare low dose (0.035 mg/day) of Vivelle with placebo in patients suffering from moderate to severe hot flushes associated with menopause. The plan called for patients to be randomized to receive either Vivelle or matching placebo following a two-week run-in period. After a two-week run-in period, patients who had a minimum of 7 hot flushes per 24 hours or 60 hot flushes per week were eligible for randomization.

A total of 259 patients were randomized, with 130 assigned to Vivelle and 129 assigned to placebo. Two patients had unsatisfactory therapeutic effect and were not considered efficacy analyzable patients. A total of 257 patients were considered valid for *intent-to-treat* analyses (with at least one application) and a total of 242 patients were considered for *acceptable* patient analyses (who did not meet the inclusion criteria of moderate to severe hot flushes during the 10 days of 2-week run-in period).

Patients were instructed to record the number and severity of hot flushes during the day and night in the patient diary. Patients were also instructed to provide evaluation of the treatment

effectiveness at the end of each of the three 28-day treatment cycles (during the double-blind treatment phase of 12-week). Severity of hot flushes were recorded on a 4-point qualitative scale (0=none, 1=mild, 2=moderate, and 3=severe) and a global evaluation was recorded on a 7-point scale (1= very much improved,.....,7=very much worse; compared to pre-treatment condition).

The study was designed (with 80% power) to detect a mean difference of 2.0 hot flushes/day between placebo and Vivelle. The *primary endpoint* was the change from baseline in mean hot flushes/day in the last two weeks of the first treatment cycle. Baseline values were recorded during the 2-week run-in period. The *secondary endpoints* were the severity of hot flushes at the end of each treatment cycle and a global evaluation made at the end of treatment.

II.2. Sponsor's Analysis Plan

The sponsor's analysis plan included an acceptable patient analysis, excluding those patients with less than 10 days of moderate to severe hot flushes during the run-in period, and an intent-to-treat analysis, including all patients with at least one application of Vivelle 0.035 mg/day dose. The Vivelle vs. placebo differences in mean number of hot flushes (from baseline to last two-weeks of cycles 1, 2, and 3) were evaluated by performing analysis of covariance including treatment by baseline hot flushes as an interaction term. The between treatment analysis on the patient global level evaluation of treatment effectiveness was performed using rank sum statistics.

No imputations of the missing diary data (at baseline or post drug) were planned or performed.

II.3. Results

II.3.1. Demographic and Baseline Comparison

Based on all patients (n=259) randomized, there were no apparent differences between the Vivelle and placebo group with respect to age, ethnicity, weight, menopausal criteria, baseline hot flushes and the duration of treatment.

II.3.2. Primary Efficacy

As per protocol, the primary efficacy variable was the change from baseline (mean number of hot flushes per 24 hours in weeks 3 and 4) at the end of cycle 1. The sponsor defined intent-to-treat and acceptable patient population for efficacy but provided the results using only the acceptable patient at the end of cycle 1 and using the ITT patient at the end of cycle 2 and 3, respectively.

In this review, the primary efficacy variable was re-analyzed using the ITT patient population and then compared with the results using the acceptable patient population. There were a total of 256

intent-to-treat and 242 acceptable patients, respectively. Three patients were excluded from the ITT population and 10 additional patients were excluded from the acceptable population. Table 1 shows the efficacy results using both data sets.

Table 1
Change from Baseline in the Mean Number of Hot Flushes/24 hour in the last Two weeks of cycle 1

Treatment	Intent-to-treat (n=256)	Acceptable (n=242)
Placebo (n):	**126**	**117**
Baseline Mean (SD)	11.7(5.5)	11.4(4.8)
Post-Treat. Mean (SD)	6.8(5.6)	7.1(5.7)
Difference (SD)	-4.9(4.7)	-4.3(4.2)
Vivelle (n):	**130**	**125**
Baseline Mean (SD)	11.9(5.4)	11.6(5.2)
Post-Treat. Mean (SD)	4.0(4.2)	4.1(4.3)
Difference (SD)	-7.9(5.6)	-7.4(4.1)
P-value *vs.* Placebo	<.001	<.001

The results of our analyses using intent-to-treat patients were similar to results using acceptable patients, with the Vivelle group demonstrating a statistically significant difference from the placebo group.

II.3.3. Secondary Efficacy

The secondary efficacy variables were the changes (from baseline) in mean hot flushes at the end of weeks 8 and 12; and the severity of hot flushes at the end of weeks 4 (last two weeks of cycle 1), 8, and 12 (four weeks of cycle 2 and 3). The sponsor's analyses showed that Vivelle 0.035mg/day was significantly better than placebo in reducing the number and severity of hot flushes at the end of week 8 and 12. The sponsor also looked at the patient's qualitative global evaluation of treatment efficacy. Their analyses indicate that patients in the Vivelle group reported a much improved condition compared to placebo at the end of each treatment cycle.

III. Re-analysis of Study 1003-A

In the original submission, study 1003-A failed to demonstrate statistically significant reductions in mean hot flushes (using combined data for weeks 1st, 2nd, and 3rd of cycle 1) for the 0.035 mg/day dose group compared to placebo group ($p>0.05$). A separate analysis by the FDA Statistical reviewer (review dated 12/10/93) confirmed the similar finding that the low dose of Vivelle was not statistically better than placebo in reducing hot flushes in the first cycle of treatment. In the current submission, the sponsor re-analyzed the data for the same low dose

(0.035 mg/day of Vivelle) and placebo group with the efficacy variable being the mean hot flushes at weeks 2 and 3 combined, rather than all three weeks. This re-analysis was performed initially using ANCOVA with baseline mean, center, and treatment-by-center interaction term in the model and showed a marginally significant (p=0.0537) reduction in hot flushes in 0.035 mg/day vivelle group compared to placebo. A subsequent analysis excluding the interaction term (not significant, p>0.10) but including the center term (even though it was not significant with a p>0.67) showed a statistically significant (p=0.0196) reduction in hot flushes. Based on this analysis, the sponsor claims that the statistical significance of low dose of Vivelle using this alternative statistical model was achieved.

However, we have concern with the sponsor's re-analysis for the following reasons:

1. The efficacy results in Study 1003-A have already shown that the low dose of Vivelle was no different than placebo when analyzed appropriately (adjusting for multiple comparisons). Therefore, a post hoc look at the data would essentially be data dredging rather than a valid analysis.

2. Efficacy analysis with data reduction (week 1 response excluded) induces potential bias.

IV. Conclusion

The new Phase IV study (036) provided evidence that the low dose of Vivelle (0.035 mg/day) was statistically significantly different from placebo in reducing the severity and frequency of post menopausal hot flushes at the end of the last two weeks of the first treatment cycle. Vivelle's effectiveness was also significantly ($p<0.01$) different in the same direction at the end of weeks 8 and 12. Due to reasons specified in section III above, the conclusions drawn from the re-analysis of data from study 1003-A were statistically biased. Re-analysis did not add any new evidence that low dose of Vivelle was more effective than placebo in those patients although the results consistently trended in the same direction in all studies.

/S/ 1/10/00

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/S/

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