CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-167

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #	**21-167 Class 3-S (Type 6)**
Drug Name	**Vivelle (estradiol transdermal system)**
Sponsor	**Novartis**
Indication	**Prevention of postmenopausal osteoporosis**
Review Documents	**Volumes 1.5-1.22, 1.58 dated October 19, 1999**
	SAS datasets submitted Oct. 1999
Medical Reviewer	**Bruce Schneider, M.D. (HFD-510)**

AUG 3 2000

1. Background

Vivelle (estradiol transdermal system) was approved under NDA# 20-323 for treatment of estrogen deficiency syndrome. Specifically, treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulval and vaginal atrophy; and treatment of hypoestrogenisum due to hypogonadism, castration, or primary ovarian failure.

Last October, Novartis submitted a Type 6 NDA for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis. The sponsor included data from four (035, 036, 037, and 038) clinical studies. Study 035 was conducted in the target indication of prevention of postmenopausal osteoporosis (PMO), which is the basis for this review. According to Ms Enid Galliers, the original project manager, Study 036 was for treatment of menopausal symptoms and was included in vasomotor symptom study currently reviewed under supplement 021 by DRUDP: Studies 037 and 038, evaluated skin tolerability and adhesion profile of Vivelle compared to Climara, had been consulted to dermatologic drug product Division.

Data from published studies on Vivelle and Menorest (estradiol system identical to Vivelle marketed by Rhone-Poulenc Rorer outside the United States and Canada) are included in this submission. The sponsor stated that protocol 035 is the efficacy trial that the labeling registration would be based on and information from literature is included in the clinical trial report for Study 035.

According to the sponsor, Study 036 was undertaken to satisfy a phase IV commitment to FDA to confirm the efficacy of the lowest approved dose of Vivelle (0.0375 mg/day) in the treatment of moderate to severe postmenopausal vasomotor symptoms. A total of 259 postmenopausal women were included in this 12-week, randomized, double-blind, placebo-controlled, parallel group study. The sponsor concluded that "the results of Study 036 confirm the efficacy, safety, and tolerability of Vivelle 0.0375 mg/day in the treatment of postmenopausal vasomotor symptoms." According to Dr. Mahboob Sobhan, the original statistical reviewer, "the study provided evidence that the low dose of Vivelle —— mg/day) was statistically significantly different from placebo in reducing the severity and frequency of postmenopausal 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."

Studies 037 and 038 were phase IV trials designed to evaluate specifically the skin tolerability and adhesion potential of Vivelle (0.05 mg/day) compared to Climara, a once weekly applied patch delivering 0.05 mg of estradiol per day. These 22-day, randomized, blinded, within-patient, placebo-controlled studies included postmenopausal women at least 35 years of age. According to the sponsor, both Vivelle and Climara were well tolerated and the local skin irritation potential of both patches was low. Vivelle showed a lower frequency of erythema and other signs of local skin irritation compared to the once weekly patch, Climara.

This review pertains to evaluation of efficacy results and its corresponding labeling of protocol 035.

Keywords: NDA Review, Clinical Study.

2. Study 035

This was a randomized, modified, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and the dose-response of a new estradiol matrix transdermal therapeutic system in the prevention of postmenopausal bone loss. The study was initiated on March 14, 1995 and completed on January 13, 1999. There were seven amendments to the protocol. In the following, strikethrough of the original text or added text with the corresponding amendment # indicated these changes. There were other changes in study conduct, for instance, the trial test systems were replaced twice during the course of the trial, baseline measurement of fasting glucose was missing in 96 (37%) patients due to an inadvertently omitted measurement of fasting glucose in the serum chemistry test identified approximately 18 months after trial initiation.

Primary Objectives:

(1) to demonstrate the efficacy and the dose-response of Vivelle with respect to the prevention of postmenopausal bone loss of the lumbar spine in ~~——~~ (amendment VII, dated March 27, 1996) women

(2) to determine the minimum effective dose of Vivelle for the prevention of postmenopausal bone loss of the lumbar spine ~~——————~~

(3) to assess the systemic and local safety and tolerability of chronic (2 year) treatment with Vivelle in postmenopausal ~~——————~~ women

Secondary objectives:

(1) to demonstrate the efficacy and dose-response of Vivelle with respect to the prevention of postmenopausal bone loss of the femoral neck and whole body with Vivelle

(2) to assess the effects of Vivelle, compared to that of placebo, on urinary excretion of cross-linked N-telopeptides of type I collagen (NTx), and serum osteocalcin,

(3) to assess the correlation between the changes in the bone mineral density (BMD) and changes in the urinary/serum concentrations of the above markers of bone turnover in postmenopausal patients treated with Vivelle and placebo

Eligible postmenopausal women were randomized to receive either placebo or one of the four Vivelle doses: 0.025 mg/day (7.25 cm^2), 0.0375 mg/day (11 cm^2), 0.05 mg/day (14.5cm^2), or 0.10 mg/day (29 cm^2) in ~~20~~ centers. The trial was blinded with respect to the treatment (active or placebo) only, and not to the dose levels of the active treatment (amendment V, February 08, 1996). The patients applied the trial treatment systems to buttock or abdomen, twice a week, for a total of two years. The patients were seen in the clinic for the post-treatment evaluations after 3, 6, 12, 18, and 24 months of the trial treatment (visits 3, 4, 5, 6, and 7, respectively), see schematic diagram (Appendix I in p.9). Patient stratification by hysterectomy status was added in amendment VII.

According to the sponsor, Vivelle 0.05 mg/day and 0.1 mg/day were selected based on the known efficacy and safety of Estraderm (estradiol transdermal therapeutic system) 0.05 mg and 0.1 mg per day in the prevention of postmenopausal osteoporosis. The two lower doses of Vivelle (0.0375 mg/day and 0.025 mg/day) were included in this dose-ranging trial to establish the minimum effective dose of the test system.

Approximately 36 patients per treatment arm who completed the 2-year study were planned. Sample size was calculated based on the percentage change in bone mineral density of the lumbar spine as measured by DPA for a group of Estraderm treated patients (variance = 33%). It is noted that a completed patient is defined as a patient who meets all inclusion/exclusion criteria and completes the 2 year trial or discontinues the trial prematurely due to significant bone loss or endometrial hyperplasia (amendment VII), to be commented in the Reviewer's Assessment on Robustness of the Results and Comments paragraph, see p.4.

As stated in the original protocol, bone markers would be analyzed based on change from baseline, which was later changed to % change from baseline prior to unblinding the trial. Therefore, the primary efficacy variable was the % change from baseline in BMD of the anterior/posterior lumbar spine (L1-L4, AP), as measured by DEXA. Secondary efficacy variables were (1) % change from baseline in BMD of the lateral lumbar spine (L2-L4, lateral), (2) % change from baseline in BMD of the femoral neck, (3) % change from

baseline of the total body mineral content (BMC), (4) % change in serum osteocalcin from baseline, (5) % change in urinary NTx creatinine ratio from baseline.

Statistical analysis plan: No interim analysis was planned. The primary analysis was the % change in BMD of the anterior/posterior spine (L1-L4) from baseline at visit 7 (week-104) for the intent-to-treat patients.

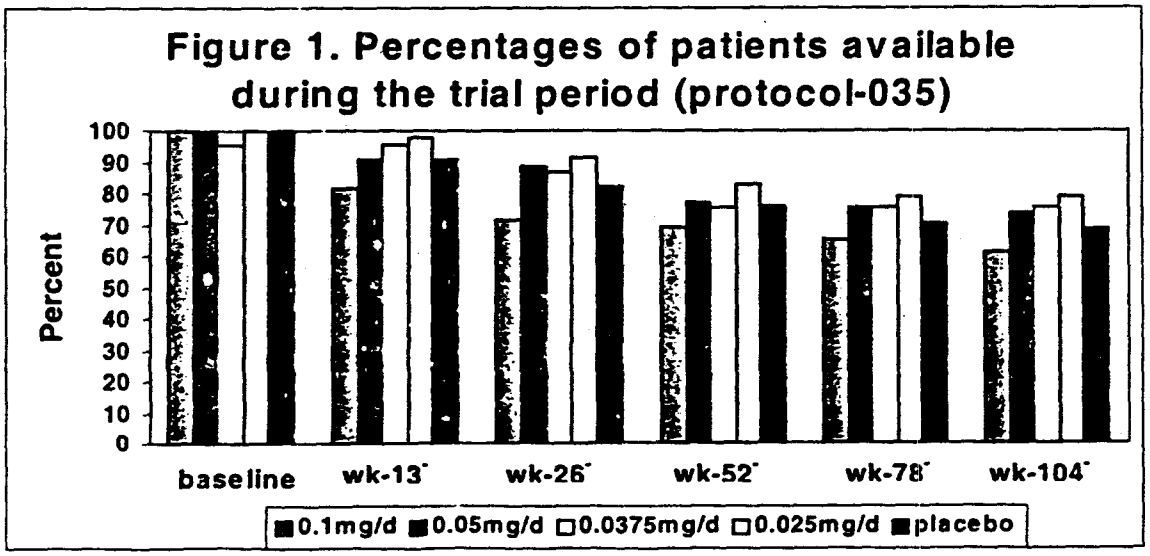
Time from randomization	Inclusion in analysis*	Labeled as
> 3 months to ≤ 9 months	Visit 4 analysis	Week-26
> 9 months to ≤ 15 months	Visit 5 analysis	Week-52
> 15 months to ≤ 21 months	Visit 6 analysis	Week-78
> 21 months	Visit 7 analysis	Week-104

* last observation carried forward approach was used for early discontinued patients (revision of LOCF who discontinued prematurely due to endometrial hyperplasia/cancer, amendment VII) as an exploratory analysis.

Statistical model was the two-way analysis of covariance (ANCOVA) including the main effects of treatment, center, and interaction with covariate of average baseline measurement. Treatment-by-baseline was also included to test for the homogeneity of the regression slope between the treatment groups. Between-treatment comparisons of the active treatment groups vs. placebo were performed using Dunnett's multiple comparison procedure using an overall 0.05 level of significance (2-sided). Between-treatment comparisons of the active treatment groups were performed using t-tests and the pooled error term from the analysis of covariance at the nominal 0.05 level of significance (2-sided). If distributional problems were encountered (lack of normality), between-treatment comparisons were to be made by using non-parametric methods.

3. Results

A total of 261 eligible postmenopausal patients were randomized to receive Vivelle 0.1mg/d (n=49), 0.05mg/d (n=53), 0.0375mg/d (n=45), 0.025mg/d (n=47) or placebo (n=67). From Table 1 listed in p.10, it was observed that more patients discontinued the study early in the highest dose Vivelle (39%), followed by placebo (31%), 0.05mg/d Vivelle (26%), 0.0375mg/d Vivelle (24%), and 0.025mg/d Vivelle arm (21%). As shown in Figure 1, slightly less than 20% of the randomized patients were discontinued prior to 13 weeks (about 3 months of treatment) with the 0.1mg/d Vivelle, which was twofold to nine-fold higher than the other four treatment arms. Major difference between this highest dose Vivelle arm and the remaining arms was the reason of discontinuation due to adverse experience: 25% in 0.1mg/d Vivelle, ~9% in 0.05mg/d, 0.0375mg/d, and 0.025mg/d Vivelle, and 3% in placebo.



Reviewer Evaluation and Comments:

From this reviewer's evaluation, baseline characteristics were similar in age (51-52 years), body mass index (28), race (white: 90% in Vivelle and 94% in placebo), percent hysterectomized (60% in Vivelle and 64% in placebo). There were numerical imbalances seen in the percent smoking (20% in Vivelle and 10% in placebo) and type of menopause (natural: 84% in Vivelle and 73% in placebo) at baseline based on all randomized patients

Primary Efficacy - % change from baseline at week-104 (2-year) of AP lumbar spine BMD

As summarized in Table 2 (sponsor's post-text table 9.1-1A, post-text table 9.1-1B, and Table 1.34 of Appendix 5) listed in p.11, percent change from baseline in AP lumbar spine BMD at week-104 was nominally significantly different from zero for each of the study arms, p<0.001, <0.001, 0.002, 0.011 and <0.001 for Vivelle 0.1mg/d, Vivelle 0.05mg/d, Vivelle 0.0375mg/d, Vivelle 0.025mg/d, and placebo, respectively. Numerically, Vivelle was shown to increase the AP lumbar spine BMD whereas placebo was shown to decrease the AP lumbar spine BMD when compared to their corresponding baseline lumbar spine BMD. As for the difference between each treatment arm versus placebo, it appeared that percent change from baseline in AP lumbar spine BMD at year-2 of all Vivelle treatment groups were shown to be significantly different from placebo: least square mean of 6.22% with Vivelle 0.1mg/d (p<0.001), 2.72% with Vivelle 0.5mg/d (p<0.001), 0.99% with Vivelle 0.0375mg/d (p=0.024), and 1.34% with Vivelle 0.025mg/d (p=0.002) compared with placebo of least square mean of -2.4%. Between the Vivelle dosages, however, Vivelle 0.1mg/d was shown significantly different from each of the three lower dosages ($p \leq 0.003$), and no statistically significant differences were observed among these lower dosages: 0.05mg/d, 0.0375mg/d, and 0.025mg/d, as summarized in Table 3 (listed in p.13). These results were based on patients' having at least one post baseline measurement and were verified by this reviewer.

The sponsor also conducted an "exploratory analysis" based on the last observation carried forward (LOCF) for all randomized patients, as summarized in Table 2R (sponsor's Table 1.36 of Appendix 5) and Table 3R (sponsor's Table 1.37 of Appendix 5), listed after Appendix in p.12 and p.14. These results were also verified by this reviewer.

Reviewer's Assessment on the Robustness of the Results and Comments:

Statistical model specified in the protocol was 2-way ANCOVA with treatment, center, interaction, and baseline measurement as the covariate. The model used in the NDA submission was 1-way ANCOVA on % change from baseline. According to the sponsor, center was not included in the model as all of the efficacy data were analyzed by one central laboratory _____ and as center-by-treatment cell size was anticipated to be small.

- The sponsor considered the intent-to-treat population as those patients who had baseline measurement and had at least one post-baseline measurement.

Table 4. Distribution of patients used in the all randomized vs. those used in the all ITT reported by sponsor

	Viv 0.1mg/d	Viv 0.05mg/d	Viv 0.0375mg/d	Viv 0.025mg/d	Placebo
# randomized (N=261)	49	53	45	47	67
# with baseline only (N=81)	20 (41%)	16 (30%)	13 (29%)	10 (21%)	22 (33%)
# used in sponsor's ITT (N=(180)	29 (59%)	37 (70%)	32 (71%)	37 (79%)	45 (67%)
# reported by sponsor as ITT (N=239)	42 (86%)	48 (91%)	41 (91%)	47 (100%)	61 (91%)

Using the primary efficacy outcome as an example, a total of 239 patients (92% of randomized patients) were reported by the sponsor as the all-ITT patients. This included 86% of the randomized patients in the 0.1mg/d arm, 91% in the 0.05mg/d arm, 91% in the 0.0375mg/d arm, 100% in the 0.025mg/d arm, and

91% in the placebo arm, please see the last row of Table 4. However, actual number of patients used in the all-ITT calculation was much less than the above stated: 59% for Vivelle 0.1mg/d, 70% for Vivelle 0.05mg/d, 71% for Vivelle 0.0375mg/d, 79% for Vivelle 0.025mg/d, and 67% for placebo, see the second to the last row of Table 4.

This reviewer found that more than 30% (81/261) of patients having only the baseline lumbar spine BMD data but no post-baseline measurements. These patients were not used in the sponsor's all-ITT analysis for the primary efficacy outcome, percent change from baseline of lumbar spine BMD at week-104. Clinical characteristics at baseline of patients included vs. excluded among the treatment arms were investigated. First, this reviewer explored potential imbalance in percent of patients hysterectomized at baseline. Results are displayed in Table 5 below.

Table 5. Percent† of patients hysterectomized in those with vs. without post-baseline lumbar spine BMD

% hysterectomized	Viv 0.1mg	Viv 0.05mg	Viv 0.0375mg	Viv 0.025 mg	placebo
W/o post-baseline N=31	11 (55%)	8 (50%)	6 (46%)	1 (10%)	5 (23%)
Had post-baseline N=115	18 (62%)	23 (62%)	16 (50%)	26 (70%)	32 (71%)
Total N=146	29 (69%)	31 (65%)	22 (54%)	27 (57%)	37 (61%)

† % relative to total number of patients in each treatment arm.

With all randomized patients, percent of patients hysterectomized ranges from 54% to 69%. These percentages were 50% to 71% among those patients who had post baseline measurement in lumbar spine BMD, not too different from those of all randomized patients. Percentages varied in those patients without post baseline measurements, 10% to 55%, these accounted for 31% of all randomized patients.

Secondly, distributions of baseline lumbar spine BMD among the five treatment groups by patients' having post-baseline measurements vs. those without having post-baseline measurements can be found in Table 6.

Table 6. Mean (standard deviation) of baseline lumbar spine BMD

Lumbar Spine BMD	Viv 0.1mg	Viv 0.05mg	Viv 0.0375mg	Viv 0.025 mg	placebo
W/o post-baseline N=81	1.04(0.16)	0.99(0.09)	0.96(0.06)	1.00(0.10)	1.02(0.16)
Had post-baseline N=180	0.97(0.09)	0.98(0.11)	1.01(0.10)	1.02(0.10)	1.02(0.13)

Within each treatment arm, there were no notable differences in the distribution of baseline lumbar spine BMD between the two subsets, viz., those without post-baseline measurements vs. those with post-baseline measurements. Within each subset, distributions of baseline lumbar spine BMD among the five treatment groups were similar. This implies that results of the primary efficacy endpoint evaluation by including all randomized patients in the all-randomized analysis and excluding slightly more than 30% of randomized patients in the all-ITT analysis would likely be similar in terms of statistical evidence, except that effect of Vivelle would be reduced with the all-randomized evaluation. This is because those patients without post-baseline measurement would have zero percent change from baseline using the last observation carried forward imputation. This conjecture was confirmed by an analysis of LOCF of all-randomized patients, as summarized in Table 2R and Table 3R, which can be found in p.12 and p.14.

In summary, least square means were 6.22% with Vivelle 0.1mg/d ($p<0.001$), 2.72% with Vivelle 0.5mg/d ($p<0.001$), 0.99% with Vivelle 0.0375mg/d ($p=0.024$), and 1.34% with Vivelle 0.025mg/d ($p=0.002$) compared with placebo of least square mean of –2.4% based on the all-ITT analysis. These estimates were 4.96% with Vivelle 0.1mg/d ($p<0.001$), 2.31% with Vivelle 0.5mg/d ($p<0.001$), 0.59% with Vivelle 0.0375mg/d ($p=0.016$), and 1.01% with Vivelle 0.025mg/d ($p=0.001$) compared with placebo of least square of –2.16% when the all-randomized analysis was performed. Results of comparison among Vivelle dosage arms showed that Vivelle 0.1mg/d was significantly different from each of the three lower dosages ($p \leq 0.007$), and no statistically significant differences were observed among these lower dosages: 0.05mg/d, 0.0375mg/d, and 0.025mg/d, as summarized in Table 3R (listed in p.14) based on the all-randomized patients.

Labeling

[redacted] of randomized subjects ([redacted] on active drug, [redacted] on placebo) contributed data to the analysis of percent change from baseline in bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable. There was an increase in BMD of the AP lumbar spine in all Vivelle dose groups; in contrast to this a decrease in AP lumbar spine BMD was observed in placebo patients."

Reviewer's Comments: The sponsor's all-ITT analysis on the lumbar spine BMD data was based on patients' having baseline lumbar spine BMD measurements and at least one post-baseline measurement, which included [redacted] , not [redacted] patients. Labeling should reflect such information, as shown in bold above.

Secondary Efficacy

- **Percent change from baseline in AP lumbar spine BMD at visit-4 (week-26), visit-5 (week-52), and visit-6 (week-78)**

From Figure 9.1-1 of the sponsor (see p.15 after Appendix), except that Vivelle 0.05mg/d was not shown to be significantly different from placebo (p=0.097) at visit-4, the difference in % change from baseline in AP lumbar spine BMD between Vivelle and placebo was nominally significant and increased at and after visit-4 with $p \leq 0.024$. Among the Vivelle doses, the results for visit-5 and visit-6 were consistent with the results for visit-7 (week-104) as described under the primary efficacy.

Labeling

"All Vivelle doses were significantly superior to placebo (P<0.05) at all time points with the exception of Vivelle 0.05 mg/day at 6 months, [redacted] ,

Reviewer's Comments: Vivelle treated patients were not shown to have significantly different mean percent change from baseline of AP lumbar spine BMD at 6 months compared to those patients not receiving any Vivelle treatment at 6 months (p=0.097). This result does not imply bone preservation etc. Thus, statement of 'implying ....' should be deleted.

- **Lateral Lumbar Spine BMD**

Only Vivelle 0.1 mg/day dose group showed a nominally significant difference from placebo in lateral lumbar spine BMD at week-104 and earlier visits. The three lower dose groups of Vivelle were not statistically distinguishable from placebo. Percent change from baseline at week-26, week-52, week-78, and week-104 were depicted in the sponsor's Figure 9.2-1 (see p.15 after Appendix).

- **Femoral Neck BMD**

All doses of Vivelle were nominally significantly superior to placebo with respect to percent change from baseline at week-104 in femoral neck BMD. Vivelle 0.1mg/day dose group was superior to placebo at week-26 up to week-104. The other dose groups showed a mixture of significant and non-significant results when compared to placebo at these visits. It was not clearly demonstrated that Vivelle 0.1mg/day dose group is superior to the remaining dose groups based on evaluation of femoral neck BMD. Graphical display over these visits can be found in the sponsor's Figure 9.2-2 (see p.16 after Appendix).

Labeling

"Analysis of percent change from baseline in femoral neck BMD — showed similar results; all doses of Vivelle were significantly superior to placebo ($p<0.05$) at 24 months." **There were no clear differences among Vivelle doses in femoral neck BMD.**

Reviewer Comments: The above labeling reflects appropriately of the finding from the data collected. However, since Vivelle 0.1mg/d dose group was not clearly shown to be superior to the remaining dose groups, this reviewer suggests to add the bolded test as above.

- **Total Body BMC (Bone Mineral Content)**

All doses of Vivelle were nominally significantly superior to placebo with respect to percent change from baseline in total body bone mineral content. However, Vivelle dose groups were not shown to be statistically significantly different with such measure. Percent change from baseline of total body BMC over time were displayed in the sponsor's Figure 9.2-3 (see p.16 after Appendix).

- **Serum osteocalcin**

As depicted in the sponsor's Figure 9.2-4 (see p.17 after Appendix), least square mean of percent change from baseline was plotted against treatment duration. At week-104, serum osteocalcin showed a decrease from baseline for the Vivelle 0.1mg/d, 0.05mg/d, and 0.025 mg/d dose groups, but an increase for the Vivelle 0.0375mg/d and placebo groups. There were no nominally significant differences between any of the Vivelle doses and placebo.

Labeling

[redacted]

Reviewer Comments: Since serum osteocalcin was a secondary efficacy and was not supported by statistical tests, this reviewer suggests that this paragraph be removed.

- **Urinary NTx creatinine ratio**

Similar to what was observed in the serum osteocalcin, urinary NTx creatinine ratio was not shown to be nominally significantly different between any Vivelle dose group and placebo at week-104. The sponsor's Figure 9.2-5 (see p.17 after Appendix) presented the least square mean of percent change from baseline over treatment duration.

4. Summary

Protocol 035 was a randomized, modified, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and the dose-response of a new estradiol matrix transdermal therapeutic system in the prevention of postmenopausal bone loss. Patients were blinded to the received treatment of Vivelle or placebo, however, patients were not blinded to the dosage level administered. Of the 261 randomized patients, a little more than 30% (81 patients) having only the baseline lumbar spine BMD were not included in the sponsor's all-ITT analysis.

Within each treatment arm, there were no notable differences in the distribution of baseline lumbar spine BMD between the two subsets, viz., those without post-baseline measurements vs. those with post-baseline measurements. Within each subset, distributions of baseline lumbar spine BMD among the five treatment

groups were similar. It appeared that results of the primary efficacy outcome of percent change from baseline at week-104 in lumbar spine BMD based on all-randomized analysis and those on all-ITT analysis were similar in terms of statistical evidence, but was less profound in the all-randomized analysis. On average, Vivelle 0.1mg/day treated patients were shown to significantly improve their lumbar spine BMD (4.96%) than Vivelle 0.05mg/day (2.31%), 0.0375mg/day (0.59%), and 0.025mg/day (1.01%) based on the all-randomized patients. Dose-response of Vivelle with respect to the prevention of postmenopausal bone loss of the lumbar spine in women, one of the primary objectives, appeared that Vivelle 0.1mg/day was significantly different from the remaining three dosages. Adverse experience reporting was more than twofold in the Vivelle 0.1mg/day dose group (25%) than those of the remaining three dose groups (~9% in 0.05mg/day, 0.0375mg/day, and 0.025mg/day, respectively), was more than eightfold than the placebo treated patients (3%).

5. Conclusion

While slightly more than 30% of randomized patients were not included in the sponsor's all-ITT analysis, distributions of baseline lumbar spine BMD were similar among the Vivelle dose groups and the placebo overall or by their having or without having the post-baseline measurement of lumbar spine BMD. This double-blind, modified, placebo controlled trial showed that significant improvement on percent change from baseline of lumbar spine BMD at week-104 was observed in all the four Vivelle dose groups compared to placebo. However, this highest Vivelle dose treated patients were found to be much more likely to withdraw from the study early due to adverse experiences than those of the remaining doses, and those of the placebo treated patients.

/S/ June 06, 2000

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SWANG/06-06-2000/Vivelle_nda
This review consists of 17 pages, which includes 8 Tables, 7 Figures and one appendix.

Appendix: Schematic Diagram (extracted from p.24 of vol#5.59).

The following is a tabular summary of the trial procedures and schedule:

Phase	**Screen**	*Double-Blind Treatment*					
Visit	1	2	3	4	5	6	7
Trial Period	Wk -1 to -3	Day 1	Wk 13	Wk 26	Wk 52	Wk 78	Wk 104
Informed Consent	X						
Medical History	X						
Complete Phys./Gyn. Exam	X						X
Interim Exam		X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X
Electrocardiogram	X						
X-ray – Thoracic Lumbar Spine	X						
Lab Safety Tests	X				X		X
Lab Screening Tests	X						
Papanicolaou Smear	X				X		X
Mammography	X				X		X
Endometrial Biopsy (if uterus intact)	X						X
BMD: Lumbar Spine, Femoral Neck	X			X	X	X	X
BMC: Total Body	X				X		X
Bone Markers	X		X	X	X	X	X
Randomization		X					
Dispense Medications		X	X	X	X	X	
Vaginal Bleeding Assessment (if uterus intact)			X	X	X	X	X
Adverse Experiences		X	X	X	X	X	X
General Instructions on Physical Exercise	X	X	X	X	X	X	X
Termination Sheet							X

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Table 1. Patient disposition by treatment group (All randomized patients)

	Vivelle 0.1 mg/day (N=49) N (%)	Vivelle 0.05 mg/day (N=53) N (%)	Vivelle 0.0375 mg/day (N=45) N (%)	Vivelle 0.025 mg/day (N=47) N (%)	Placebo (N=67) N (%)
No. randomized	49 (100.0)	53 (100.0)	45 (100.0)	47 (100.0)	67 (100.0)
No. completed	30 (61.2)	39 (73.6)	34 (75.6)	37 (78.7)	46 (68.7)
No. treated	49 (100.0)	53 (100.0)	45 (100.0)	47 (100.0)	67 (100.0)
No. discontinued	19 (38.8)	14 (26.4)	11 (24.4)	10 (21.3)	21 (31.3)
Reasons for discontinuations					
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse experience(s)	12 (24.5)	5 (9.4)	4 (8.9)	4 (8.5)	2 (3.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)
Does not meet protocol criteria	1 (2.0)	1 (1.9)	0 (0.0)	0 (0.0)	2 (3.0)
Other	6 (12.2)	8 (15.1)	7 (15.6)	6 (12.8)	15 (22.4)
In primary efficacy analysis					
All intent-to-treat patients	**42 (85.7)**	**48 (90.6)**	**41 (91.1)**	**47 (100.0)**	**61 (91.0)**
All acceptable for efficacy patients	42 (85.7)	45 (84.9)	41 (91.1)	46 (97.9)	60 (89.6)
In safety analysis					
Adverse event evaluation	49 (100.0)	53 (100.0)	43 (95.6)	47 (100.0)	67 (100.0)
Safety laboratory evaluation	49 (100.0)	53 (100.0)	43 (95.6)	47 (100.0)	67 (100.0)

Source: Post-text table 7.1-1

Table 2. Bone mineral density (g/cm**2) - L1-L4 AP lumbar spine (primary efficacy outcome)
Summary of percent change from baseline, pairwise comparisons (treatment vs. placebo) at week 104
(All intent-to-treat patients)

	Pairwise contrasts				
Percent change from baseline	Vivelle 0.1 mg/day	Vivelle 0.05 mg/day	Vivelle 0.0375 mg/day	Vivelle 0.025 mg/day	placebo
n	29	37	32	37	45
mean (SD)	5.92(3.4)	3.28(4.1)	2.00(3.4)	1.81(4.1)	-1.98 (3.6)
p-value*	<0.001	<0.001	0.002	0.011	<0.001
mean(adjusted)	6.22	2.72	0.99	1.34	-2.42
Least squares mean (=Vivelle - placebo)	8.65	5.14	3.41	3.76	
95% C.I.	(5.93,11.36)	(2.38,7.90)	(0.33,6.49)	(1.09,6.43)	
P-value**	<0.001	<0.001	0.024	0.002	

* test for the null hypothesis that the percent change from baseline is zero.
** test for the null hypothesis that Vivelle is no different from placebo
Source: Post-text table 9.1-1A, Post-Text table 9.1-1B, Table 1.34 in Appendix 5, and Table 3.1-1 of Vol.1
Pairwise contrast = difference (treatment LS mean - placebo LS mean), C.I. = confidence interval

Table 2R. Bone mineral density (g/cm**2) - L1-L4 AP lumbar spine (primary efficacy outcome)
Summary of percent change from baseline, pairwise comparisons (treatment vs. placebo) at week 104
(All randomized patients)

	Pairwise contrasts				
Percent change from baseline	Vivelle 0.1 mg/day	Vivelle 0.05 mg/day	Vivelle 0.0375 mg/day	Vivelle 0.025 mg/day	placebo
n	49	53	45	47	67
mean (SD)	4.80(4.1)	2.93(3.7)	1.46(3.3)	1.60(4.0)	-1.89 (3.4)
p-value*	<0.001	<0.001	0.005	0.008	<0.001
mean(adjusted)	4.96	2.31	0.59	1.01	-2.16
Least squares mean (=Vivelle - placebo)	7.12	4.47	2.75	3.17	
95% C.I.	(5.01, 9.23)	(2.31,6.63)	(0.38,5.12)	(0.99,5.35)	
P-value**	<0.001	<0.001	0.016	0.001	

* test for the null hypothesis that the percent change from baseline is zero.
** test for the null hypothesis that Vivelle is no different from placebo
Source: Table 1.36 in Appendix 5
Pairwise contrast = difference (treatment LS mean - placebo LS mean), C.I. = confidence interval

Table 3. Bone mineral density (g/cm**2) - L1-L4 AP lumbar spine (primary efficacy outcome)
Summary of pairwise comparisons (between doses of Vivelle) at week 104
(All intent-to-treat patients)

	Pairwise contrasts					
Percent change from baseline	Vivelle 0.1 mg/day vs Vivelle 0.05 mg/day	Vivelle 0.1 mg/day vs Vivelle 0.0375 mg/day	Vivelle 0.1 mg/day vs Vivelle 0.025 mg/day	Vivelle 0.05 mg/day vs Vivelle 0.0375 mg/day	Vivelle 0.05 mg/day vs Vivelle 0.025 mg/day	Vivelle 0.0375 mg/day vs Vivelle 0.025 mg/day
Least squares mean	3.50	5.23	4.89	1.73	1.38	-0.35
95% C.I.	(1.20,5.81)	(2.68,7.78)	(2.65,7.12)	(-0.85,4.31)	(-0.89,3.65)	(-2.86,2.17)
P-value	0.003	<0.001	<0.001	0.187	0.231	0.786

Source: Post-text table 9.1-1B
Pairwise contrast = difference (higher dose LS mean - lower dose LS mean), C.I. = confidence interval

Table 3R. Bone mineral density (g/cm**2) - L1-L4 AP lumbar spine (primary efficacy outcome)
Summary of pairwise comparisons (between doses of Vivelle) at week 104
(All randomized patients)

	Pairwise contrasts					
Percent change from baseline	Vivelle 0.1 mg/day vs Vivelle 0.05 mg/day	Vivelle 0.1 mg/day vs Vivelle 0.0375 mg/day	Vivelle 0.1 mg/day vs Vivelle 0.025 mg/day	Vivelle 0.05 mg/day vs Vivelle 0.0375 mg/day	Vivelle 0.05 mg/day vs Vivelle 0.025 mg/day	Vivelle 0.0375 mg/day vs Vivelle 0.025 mg/day
Least squares mean	2.65	4.37	3.95	1.72	1.30	0.42
95% C.I.	(0.73,4.58)	(2.29,6.44)	(2.01,5.89)	(-0.40,3.83)	(-0.68,3.27)	(-2.54,1.70)
P-value	0.007	<0.001	<0.001	0.111	0.198	0.697

Source: Table 1.37 of Appendix 5
Pairwise contrast = difference (higher dose LS mean - lower dose LS mean), C.I. = confidence interval

Figure 9.1–1
Bone mineral density – AP lumbar spine (L1–L4)
Least squares means of percent change from baseline versus treatment duration
(All intent–to–treat patients)

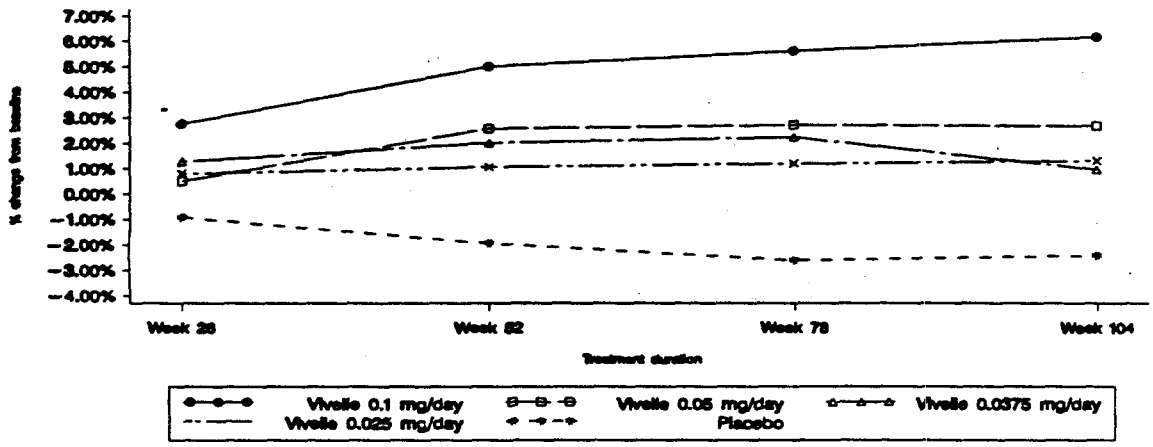

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Figure 9.2–1
Bone mineral density – lateral lumbar spine (L2–L4)
Least squares means of percent change from baseline versus treatment duration
(All intent–to–treat patients)

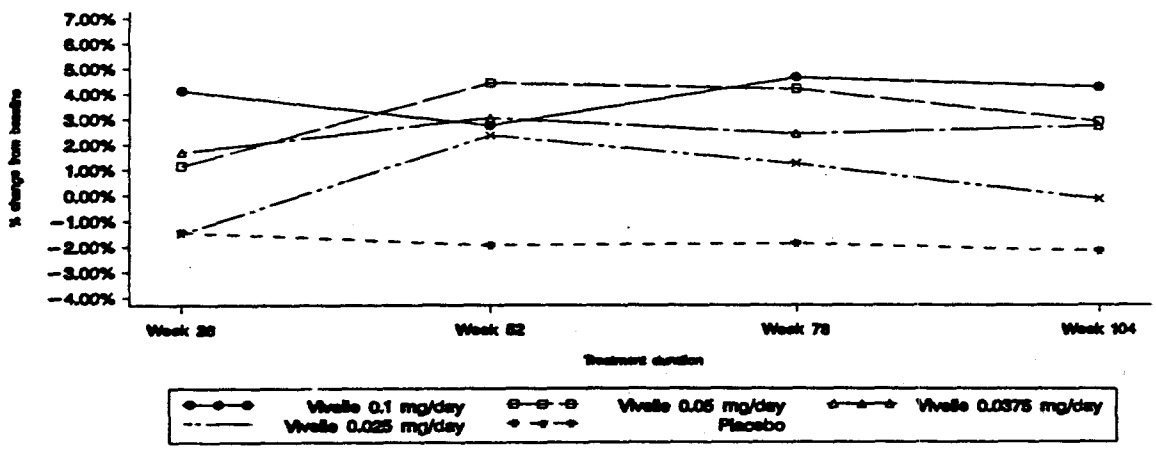

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Figure 9.2-2
Bone mineral density – femoral neck
Least squares means of percent change from baseline versus treatment duration
(All Intent-to-treat patients)

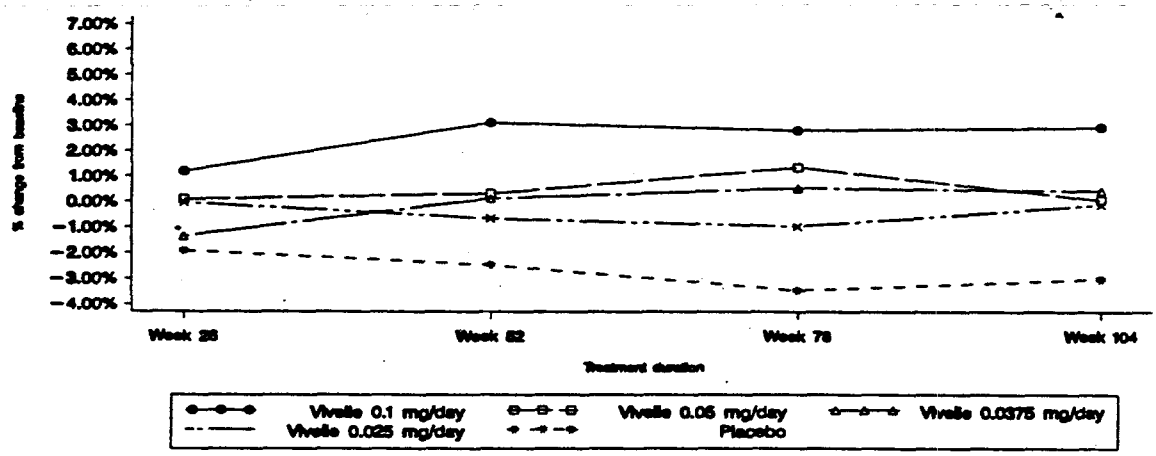

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Figure 9.2-3
Whole body bone mineral content
Least squares means of percent change from baseline versus treatment duration
(All Intent-to-treat patients)

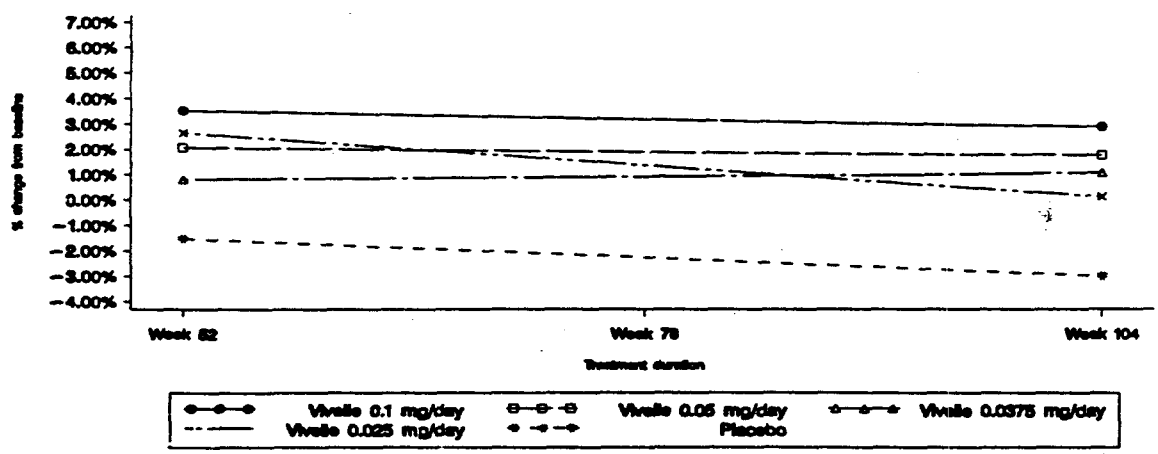

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Figure 9.2–4
Serum osteocalcin
Least squares means of percent change from baseline versus treatment duration
(All intent–to–treat patients)

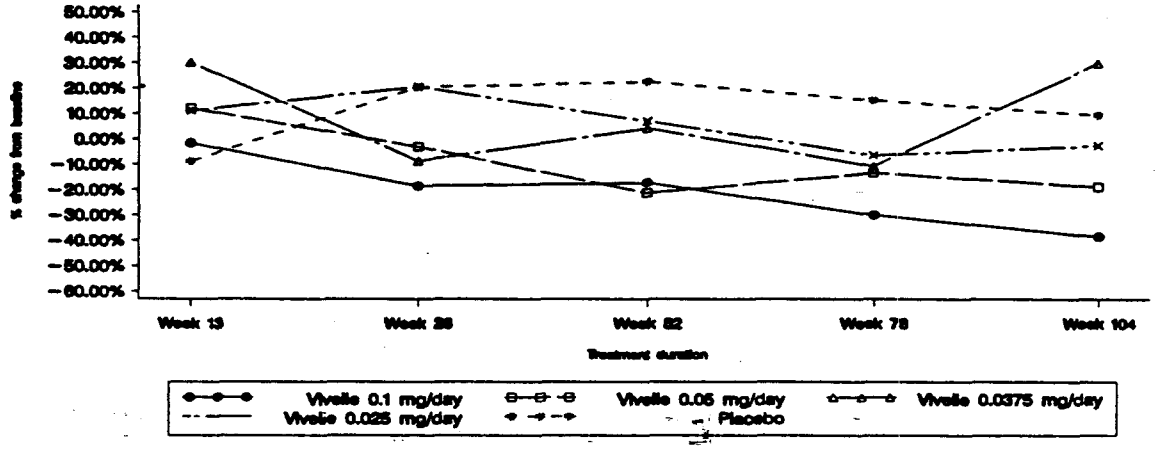

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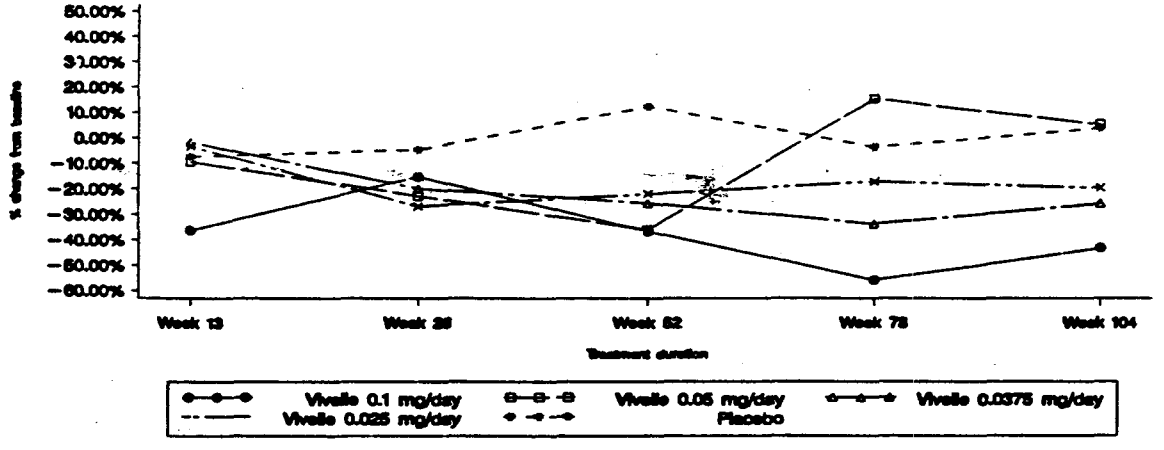
Figure 9.2–5
Urinary NTx creatinine ratio
Least squares means of percent change from baseline versus treatment duration
(All intent–to–treat patients)



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