

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-885**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 21-885

**Drug Name:** Climara Pro (17- $\beta$  estradiol and levonorgestrel) transdermal

**Indication(s):** Prevention of postmenopausal osteoporosis in women 

**Applicant:** Berlex Laboratories, Inc.

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# 1. Introduction<sup>1</sup>

## 1.1 Overview

Climara Pro is a transdermal patch (22 cm<sup>2</sup>) containing 4.4 mg of estradiol (E2) and 1.39 mg of levonorgestrel (LNG) and applied weekly during a 28-day cycle. The patch delivers 0.045 mg per day of estradiol and 0.015 mg per day of levonorgestrel. The patch was approved in 2003 for the treatment of moderate to severe vasomotor symptoms associated with menopause.

With this application, Berlex is seeking an indication for prevention of osteoporosis in women with intact uteri based on the results of two phase 3 clinical trials; Studies A09585 and A10079. These two trials were selected because they contain at least one treatment arm with an estradiol dose of 0.045 mg per day (see Table 2.1.1 on the following page for details on the treatment arms). Study A09585 is presented to show that the estrogen component of Climara Pro prevents BMD loss. Study A10079 is presented to show that the addition of LNG (higher doses than in Climara Pro) to estrogen does not diminish the effect of E2 on BMD. So in Study A09585, the goal is to show that the 0.045 mg/day dose of E2 is superior to placebo with regard to improving BMD while in Study A10079, the goal is to show that the improvement in BMD is comparable regardless of the dose of LNG and, furthermore, that these results are consistent with the results of Study A09585.

Only the results of Study A09585 are included in the labeling for Climara Pro. At a pre-NDA meeting with the applicant, FDA agreed that Study A09585 was the pivotal study and that Study A10079 was a supportive study. Therefore this reviewer has primarily focussed on the results of Study A09585 (Section 2.2 of this review). In Section 2.1, the patient populations of both Studies A09585 and A10079 are described in parallel to provide a context for the results presented in Section 2.3.

## 1.2 Data Sources

The applicant has provided SAS datasets for only Study A09585 in \\Cdsesub1\21885\N\_000\2005-02-28\crt\datasets\A09585. BMD results for approved transdermal products was extracted from labeling in the PDR.

Analyses of total lumbar spine BMD, the primary endpoint, and total hip BMD, a secondary endpoint, for Study 09585 were performed by this reviewer and so tables and graphs of these results were created by the reviewer. For other secondary endpoints, such as, biochemical markers of bone metabolism, only the applicant's results are presented.

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<sup>1</sup> Due to the brevity of the review of this supplement, the statistical template has been simplified.

## 2. Evaluation of Efficacy

### 2.1 Description of design and trial participants in Studies A09585 and A10079

Studies A09585 and A10079 were both double-blind, randomized, parallel-group, multicenter studies (Table 2.1.1). The three treatment arms in Study A09585 were 2 doses of an estradiol patch (0.0225 and 0.045 mg/day) and a placebo patch. The three treatment arms in Study A10079 were 0.045 mg/day E2+0.30 mg/day levonorgestrel patch, 0.045 mg/day E2+0.40 mg/day levonorgestrel patch and a placebo patch. Post-menopausal women were to be followed for 26 cycles, approximately 2 years. BMD was measured at baseline, and at Cycles 6, 13, 19, and 26. The primary endpoint was percent change from baseline in total lumbar spine BMD at Cycle 26.

Table 2.1.1 Clinical Trials

Study (# of centers)	Design	Treatment groups (N)	Duration of treatment
Report A09585 Prot. 96041 (19 US)	DB, randomized, parallel-group in hysterectomized women	0.0225 mg/day E2 (45) 0.045 mg/day E2 (44) Placebo (61)	26 cycles of 28 days each
Report A10079 Prot. 12226 (3 Denmark)	DB, randomized, parallel-group, double- dummy in women with intact uteri	0.045 mg/day E2+0.30 mg/day levo (69) 0.045 mg/day E2+0.40 mg/day levo (72) Placebo (71)	26 cycles of 28 days each

The entry criteria for the two trials are summarized in Table 2.1.2 below with the primary difference being that hysterectomized women were enrolled in Study A09585 while only women with intact uteri were enrolled in Study A10079.

Table 2.1.2 Entry Criteria

	Study A09585	Study A10079
Hysterectomy?	Y	N intact uterus w/endometrial thickness<5 mm
Menopause	Surgical or Evidence of ovarian failure for 1-5 years and FSH>40 and estradiol<20	1-10 years after menopause
Age	≥45 or ≥40 w/oophorectomy	45-65 or 40-65 w/oophorectomy
BMD lumbar spine	t-score≥-2.5 (Hologic≥0.81 or Lunar≥0.9)	t-score -2.5 to -1
Fracture	None within 6 months of start	None within 6 months of start

The baseline data for the women enrolled in the two trials are summarized below in Table 2.1.3. The treatment groups were well-balanced so only the overall data is shown for each study; for more details see Dr. Stadel's clinical review or the study reports in the EDR (\\Cdscsub1\m21885\N\_000\2005-03-08\clinstat).

The study populations are similar in mean age but differ on all other parameters shown here. This reviewer looked at the relationship among years post-menopausal, E2 and T-score in Study A09585 and found no relationship among the measures with r-squared values less than 5%.

Table 2.1.3. Patient Demographics for All Randomized Patients  
 Extracted from applicant's study reports

	Study A09585 (n=150)	Study A10079 (n=212)
Age (yrs)		
Mean (SD)	51 (7)	55 (3)
Range	40-83	47-63
Race		
% white	77%	99.5%
% black	18%	
Years post-menopausal		
1-3 yrs	31%	45%
>3-10 yrs	29%	55%
>10 yrs	41%	
T-scores		
Mean (SD)	-0.1 (1.4)	-1.2 (0.65)
Range	-2.8 to 3.9	-2.4 to 1.4
E2		
Mean (SD)	8.0 (8.2)	NA
Median	5.9	
% 5 or lower	40%	
TSH		
Mean (SD)	1.7 (0.96)	NA
Oophorectomy		
No	29%	97%
Unilateral	13%	3%
Bilateral	57%	0%

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## 2.2 Results for Study A09585

This section focuses on the results of Study A09585 to assess the efficacy of the estradiol for improving BMD.

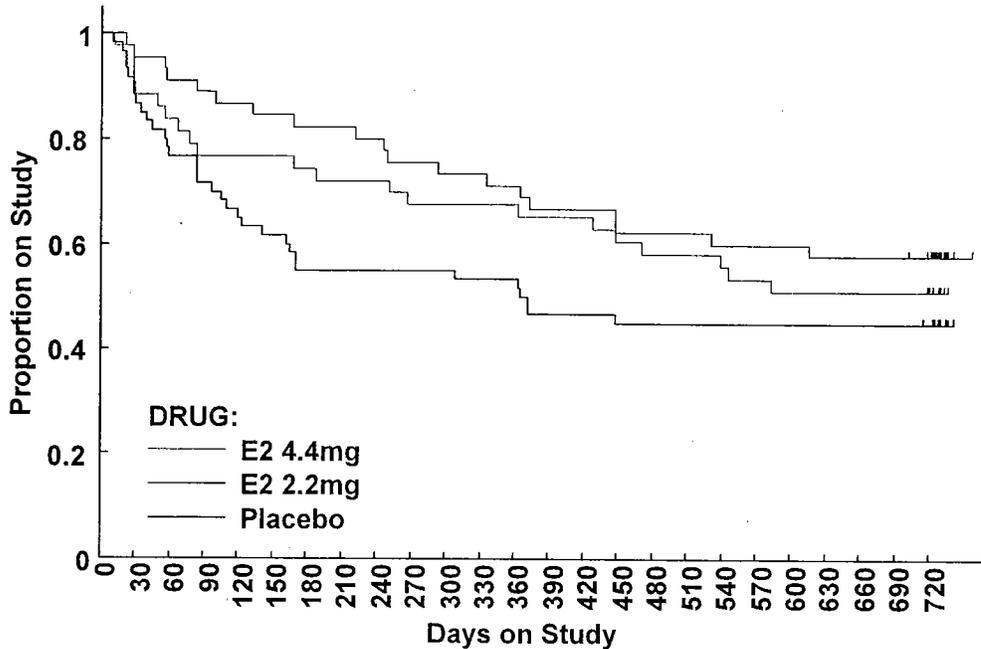
A total of a 154 patients were randomized in a 3:2:2 ratio to placebo:2.2E2:4.4E2 (Table 2.2.1). [2.2 E2 delivers 0.0225 mg /day and 4.4 E2 delivers 0.045 mg/day transdermally.] Less than half the patients completed the study with the lowest retention in the placebo group. The highest dropout rates were seen for patients under about 47 years old and for placebo patients less than 4 years from menopause.

Table 2.2.1 Study A09585 Patient Disposition

	Placebo	2.2 E2	4.4 E2
Randomized	62	45	47
Withdrew prior to baseline	-1	-0	-3
Patients with endpoint spinal BMD data	46 (74%)	38 (84%)	36 (77%)
Completers	27 (44%)	25 (55%)	22 (47%)

The graph below shows that about 20% of the patients on placebo and on 4.4 E2 discontinue from the study during about the first 3 cycles. Most of the placebo dropouts (about 45%) occur during the first 6 cycles. The treatment differences in dropout rates is quite evident.

Figure 2.2.1 Proportion of patients on study by days for each treatment group



The majority of the dropouts in the placebo group were due to an ADE or patient request (Table 2.2.2). In

the 4.4 E2 group, the major reasons for dropout were ADE and protocol violation.

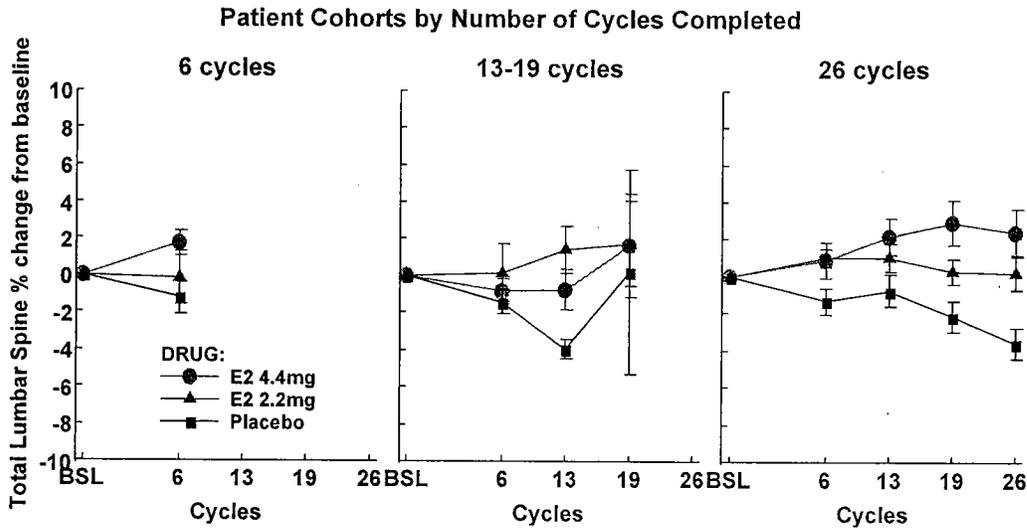
Table 2.2.2 Study A09585 Reasons for discontinuation

	Placebo (n=61)	2.2 E2 (n=45)	4.4 E2 (n=44)
ADE	16 (26%)	7 (16%)	7 (16%)
Pt/Inv request	9 (15%)	5 (11%)	3 (7%)
Prot. Viol.	3 (5%)	3 (7%)	7 (16%)
Other	6 (10%)	5 (11%)	5 (11%)

The most common adverse event leading to discontinuation was skin irritation due to the patch (8/16 placebo; 5/7 2.2 E2; 4/7 4.4 E2). In the placebo group, 5 patients discontinued for an ADE of worsening menopausal symptoms and 1 patient discontinued due to lack of efficacy. The majority of patients recorded as dropped due to “other” were lost-to-follow-up.

Due to the large number of dropouts, this reviewer first examined the total lumbar spine BMD data by cohorts of patients defined by their total time on study. Comparable treatment effects for the cohorts as illustrated in the figure below suggest that carrying forward a patient’s last-observation may be reasonable. A drawback to an LOCF analysis is that one must assume that the results for dropouts remain about the same. This seems to be a reasonable assumption for the estradiol groups but not for the placebo group where BMD continues to drop appreciably (see graph of patients completing 26 cycles). An LOCF analysis than appears to be biased against the active E2 treatment groups; however, given the low completer rate, a completer analysis will also produce biased estimates since the groups can no longer be considered randomized groups.

Figure 2.2.2 Total lumbar spine % change in from baseline for cohorts of patients defined by total number of cycles completed (Mean +/- 1 SE)



Number of patients in each cohort of graph above

Treatment Group	6 cycles	13 cycles	19 cycles	26 cycles
E2 4.4	9	6	4	18
E2 2.2	7	4	6	21
Placebo	12	6	2	25

Since the relationship of the treatments groups is the same for the three cohorts, this reviewer did not think

it was unreasonable to do an LOCF analysis. Therefore, the primary analyses were of the LOCF data and the completer data were checked for consistency.

There were two additional issues that arose regarding the integrity of the data: 1) 5 patients had BMD data that was not acceptable because of drift in the instrumentation between calibrations and so correction factors were applied to the data to account for the drift; 2) 4 patients were excluded from the applicant's ITT population due to mix-ups in the distribution of medications. The reviewer agrees with the applicant regarding the use of corrected values for data obtained when instrumentation was not properly calibrated, so corrected values were used in the computations below. Under the intent-to-treat principle, all randomized patients should be included in the analyses so this reviewer included the data from patients where the medication was switched (3 patients, 1 patient did not have data). After the switches were detected, the patients were dropped from the study and so all their available data was on randomized treatment; note that 2 patients had data for 19 cycles and 1 patient for 17 cycles.

The numbers in Table 2.2.3 differ from some of the numbers presented in the applicant's labeling which would be expected considering the additional patients included in this reviewer's analysis; however the differences are small and most likely clinically insignificant.

This reviewer has reanalyzed the BMD data for lumbar spine and hip because the medical reviewer, Dr. Stadel has recommended that these two measures go in the labeling. A highly significant treatment effect is seen of the 4.4 patch compared to placebo (treatment effect of 4.9%; least square mean difference adjusting for baseline) for total lumbar spine. The 4.4 E2 effect for the secondary endpoint of Total Hip BMD is marginally significant if one were to adjust for multiple endpoints; for example, a Bonferroni adjustment for 3 BMD endpoints (lumbar spine, hip and radius) would set alpha at 0.017. The magnitude of the effect at the hip of 2.4% (least square mean difference adjusting for baseline), however, is consistent with what has been observed for similar products (Menostar 0.014 mg/day:1.6%, Climara 0.05mg/day:~3.4%).

Table 2.2.3 Study A09585 BMD Results (Reviewer's analyses)

	Placebo (n=61)	2.2 E2 (n=45)	4.4 E2 (n=44)
Total Lumbar Spine	n=46	n=38	n=36
Baseline	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Change from baseline	-0.03 (0.04)	+0.003 (0.05)	+0.02 (0.05)
% Change from baseline	-2.9% (3.8)	+0.4% (4.2)	+1.7% (4.4)
P-value compared to placebo*		0.0007	<0.0001
% of pts with BMD change ≥ 0	27%	47%	68%
Total Hip	n=48	n=38	n=36
Baseline	0.94 (0.1)	0.97 (0.1)	0.97 (0.1)
% Change from baseline	-0.9% (5.2)	-0.2% (3.5)	+1.3% (4.2)
P-value compared to placebo*		0.49	0.02
% of pts with BMD change ≥ 0	30%	50%	59%

\* P-values are adjusted for multiple comparisons using Dunnett's correction

Twice as many patients on the high dose as on placebo show no change in BMD or an increase. Note that this categorical variable was not pre-specified.

The applicant's results for secondary endpoints show no treatment effect on BMD at the radius (Table 2.2.4). Results for bone biomarkers are inconsistent.

Table 2.2.4 Study A09585 Secondary Endpoint Results (Applicant's analyses)

	Placebo (n=61)	2.2 E2 (n=45)	4.4 E2 (n=44)
Radius midshaft BMD EP			
Baseline	0.67 (0.06)	0.65 (0.28)	0.70 (0.06)
% Change from baseline	-0.5% (5.3)	+0.5% (4.0)	-0.5% (5.5)
P-value compared to placebo		0.17	0.24
Bone biomarkers			
Change from screening			
Serum Osteocalcin	+2.9 (7.3)	-0.5 (5.9)	<b>-4.8 (7.9)</b>
Serum Alk. Phosphatase	+3.0 (5.0)	<b>-0.2 (6.2)</b>	<b>-1.9 (4.5)</b>
Deoxypyridinoline/creatinine ratio	-0.0003 (0.03)	-0.01 (0.05)	-0.02 (0.02)
Bolded sign. diff. from placebo at p<0.01			

In conclusion, the high dose group significantly increases BMD at the lumbar spine compared to placebo. Effects on BMD at the hip are marginally significant, at best, for the high dose while no treatment effect at either dose is seen at the radius.

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### 2.3 Comparison of the results for Study A09585 to the results of other studies, including Study A10079

The applicant has presented the results for Study A10079 as supportive evidence of the effect of estradiol on BMD when given with LNG. The results shown in the table below suggest that a slightly larger effect is seen when given with LNG than when given alone as in Study A09585. Though the patient populations for these trials differ in several ways (see Section 2.2 of this review), the placebo rates in the subgroup of patients post-menopausal for 3 or less years are the same suggesting that it is not unreasonable to compare these subgroup rates. What we see is a larger treatment effect (>6%) in Study A10079 than in Study A09585 (+3.7%) so the addition of LNG (as in the Climara Pro patch) does not appear to decrease the effect of the estradiol.

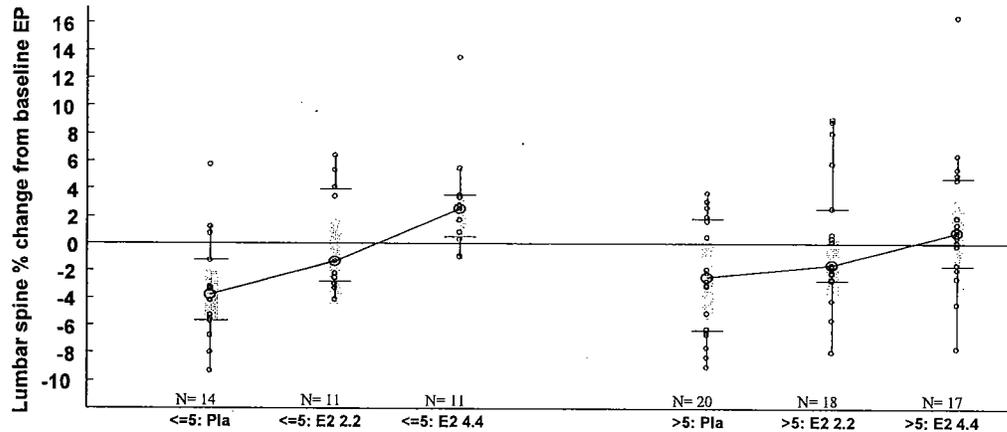
The results from studies of other products of similar dosage to the Climara dose (bolded results in table below) are consistent with the results for Study A09585 giving reassurance as to the generalizability of the results for the patch used in Study A09585 to the expected results for the Climara Pro marketed patch.

Table 2.3.1 Lumbar spine BMD results for 2 studies presented in this NDA (A09585 and A10079) and for studies presented in labeling of other products using transdermal systems of delivery

	estradiol arms	estradiol	placebo	Trt Effect
<b>Study A09585</b> hyster. (reviewer's numbers)	0.0225 mg/day	+0.4%	-2.9%	+3.2%
	<b>0.045 mg/day</b>	+1.7%		<b>+4.9%</b>
	baseline estradiol<5	+2.9%	-3.4%	<b>+6.3%</b>
	≥5	+1.5%	-2.2%	<b>+3.7%</b>
	POM >1 to 3 yrs	+1.1%	-2.6%	<b>+3.7%</b>
POM >3 to 10 yrs	+1.4%	-2.8%	<b>+4.2%</b>	
POM>10 yrs	+3.3%	-2.6%	<b>+6.1%</b>	
<b>Study A10079</b> post meno with intact uteri	<b>0.045 mg/day+LNG.3</b>			
	POM >1 to 3 yrs	+3.8%	-2.6%	+6.4%
	POM >3 to 10 yrs	+4.6%	-1.6%	+6.2%
	<b>0.045 mg/day+LNG.4</b>			
POM >1 to 3 yrs	+4.2%	-2.6%	+6.8%	
POM >3 to 10 yrs	+5.2%	-1.6%	+6.8%	
<b>Climara</b> hyster. post-meno base spine bmd>0.9	<b>0.05 mg/day (12.5 cm<sup>2</sup>)</b>	+3.8%	-2%	<b>+5.8%</b>
	0.06 mg/day (15 cm <sup>2</sup> )	+3.4%		+5.4%
<b>Vivelle-Dot</b> hyster and non- hyster ≤5yrs meno base spine≥0.827	0.0375 mg/day	+0.25%	-3%	+3.25%
	<b>0.05 mg/day</b> results for all pts combined presented in labeling (non-hyster given oral prog 2.5 mg/day)	+0.2		<b>+3.2%</b>
<b>Menostar</b> post meno with intact uteri	0.014 mg/day	+3%	+0.5%	+2.5%
	baseline estradiol<5	+3.5%	+0.3%	+3.2%
	≥5	+2.4%	+0.8%	+1.6%

The interaction of treatment and baseline estradiol level ( $\leq 5$  versus  $> 5$ ) was not statistically significant for the study overall or for the high dose-placebo comparison ( $p > 0.28$ ); the same was true for years since menopause. However the difference in magnitudes (see Table 2.3.1 and figure below) is evident and the lack of a significant interaction may be attributable to the small sample sizes.

Figure 2.3.1 Total lumbar spine % change from baseline by baseline estradiol level (boxplots and medians)



### 3. Summary and Conclusions

The applicant has submitted the results of two clinical trials to support an indication for prevention of osteoporosis for Climara Pro. A statistically significant increase in total lumbar spine, the primary efficacy variable, for E2 4.4 mg compared to placebo was seen in both trials. The results from these trials are consistent with the results reported in the labeling for similar products.

This reviewer thinks the results are adequate to support labeling. Suggestions for labeling are in the following section of this review.

#### 3.1 Labeling recommendations

Labeling recommendations here are in response to the labeling suggested by the FDA medical reviewers, Drs. Stadel and Geirhart. A clean version without changes noted is presented here.

The reasoning behind this reviewer's recommendations includes the following:

- Hip BMD was a secondary endpoint along with radius BMD. Usually the results for secondary endpoints should be treated with equal importance. However because both FDA medical reviewers recommend including the hip results in the table and so the hip results are important to prescribing physicians, this reviewer has included hip results in the proposed table below. Since hip BMD is 1 secondary endpoint out of 5 endpoints and no alpha adjustment for secondary endpoints was planned, the p-value should be reported as 0.05.
- Means graphed over time should be for completers so that the course of the response for a stable cohort is shown and not affected by changes in the patient population.
- The modifying effect of baseline estradiol levels on changes in BMD has been shown previously (e.g. Menostar) and, according to Dr. Stadel, is important clinically therefore this reviewer has added a sentence about this issue.

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