

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** NDA 21-310

**STATISTICAL REVIEW(S)**

## Statistical Review and Evaluation<sup>1</sup>

**NDA:** 21-310  
**Sponsor:** Watson Labs  
**Drug:** Alora (estradiol transdermal systems)  
**Indication:** Prevention of postmenopausal osteoporosis  
**Materials reviewed:** Hard copy submission stamp dated 1/16/01 (vol, 1.1, 1.22-1.37) and data in electronic document room  
**Medical Reviewer:** Patricia Beaston-Wimmer, M.D., Ph.D. (HFD-510)

The sponsor submitted data from one randomized, double-dummy, placebo controlled, 2-year, multicenter trial to support the use of Alora (estradiol) in the prevention of postmenopausal osteoporosis (Table 1). The trial randomized hysterectomized (with or w/o bilateral oophorectomy) postmenopausal women <70 years of age in equal numbers to three doses of Alora (.025 mg/day, .05 mg/day and .075 mg/day) and placebo. Women with prior estrogen use had a washout period of 2 months prior to randomization. The study treatment consisted of twice-weekly applications of 9 and 18 cm<sup>2</sup> patches (active and placebo) applied to the lower abdomen for twenty-six 28-day cycles. All subjects received 1000mg/day of oral calcium.

Table 1. Trial design

Study/# centers	Population	Treatment groups (# randomized)	Duration
1996023 22 US	Postmenopausal women Age <70 yrs Lumber spine BMD by >0.772g/cm <sup>2</sup> on or >0.882g/cm <sup>2</sup> on	Placebo (87) Estradiol .025 mg/day (89) Estradiol .05 mg/day (90) Estradiol .075 mg/day (89)	2 years (twenty-six 28-day cycles)

The objective of the trial was to establish the minimally effective dose that significantly prevents lumbar spine bone loss as measured by bone mineral density (BMD) when compared to placebo. BMD was measured at the lumbar spine only.

Study periods consisted of Screening, Baseline (within 28 days of Screening) and Treatment. Patient visits were scheduled at Screening and after (Treatment) Cycles 1, 3, 5, 7, 10, 13, 16, 20, 23 and 26.

The protocol-specified primary endpoint was % change from baseline in lumber

<sup>1</sup> Key words: clinical studies, NDA review, one study application, missing data

spine BMD at 2 years. Lumbar spine BMD was measured at Screening, Cycle 13 and Cycle 26 (last visit). Patients dropping prior to their scheduled Cycle 26 visit were required by protocol to have an exit lumbar spine BMD measurement. Secondary efficacy parameters were % change in lumbar spine BMD at Cycle 13 and actual change in lumbar spine BMD at Cycles 13 and 26.

BMD measurements were obtained on either \_\_\_\_\_ machines. The machines provide different BMD measurements. In order to make the baseline readings from the machines comparable, raw BMD measurements were standardized using the following algorithm:

$$\begin{aligned} \text{standardized BMD} &= 1.0755 \cdot \text{BMD} \text{ ---} \\ &= 0.9522 \cdot \text{BMD} \text{ ---} \end{aligned}$$

The primary endpoint (BMD % change) is the same for both the raw and standardized measurements.

## Results

Baseline and demographic data for all randomized patients are shown in Table 2. The mean age of patients was 53 years. Most patients were Caucasian (86%). Groups were well balanced (no statistically significant differences) with respect to all variables in Table 2 and (not shown in Table 2) BMD t score at baseline.

Table 2. Baseline and demographic data

	Placebo (n=87)	Est .025 (n=89)	Est .05 (n=90)	Est .075 (n=89)	Total (n=355)
Age (yrs)					
Mean (SD)	54 (7)	52 (8)	54 (7)	54 (7)	53 (7)
Median	54	52	53	54	54
(Min, Max)	(26, 68)	(29, 69)	(30, 69)	(36, 69)	(26, 69)
Weight (lbs)					
Mean (SD)	162 (31)	171 (38)	166 (34)	170 (36)	167 (35)
Median	161	164	163	165	163
(Min, Max)	(100, 263)	(95, 281)	(100, 255)	(103, 307)	(95, 307)
Height (in)					
Mean (SD)	64 (2)	64 (3)	64 (2)	64 (2)	64 (2)
Median	65	65	64	65	65
(Min, Max)	(60, 69)	(57, 70)	(60, 69)	(59, 70)	(57, 70)
Race					
Caucasian	74 (85%)	78 (88%)	76 (84%)	79 (89%)	307 (86%)
Black	6 (7%)	6 (7%)	7 (8%)	6 (7%)	25 (7%)
Hispanic	5 (6%)	3 (3%)	4 (4%)	1 (1%)	13 (4%)
Other	2 (2%)	2 (2%)	3 (3%)	3 (3%)	10 (3%)
Tobacco use					

Table 2, cont. Baseline and demographic data

Never used	41 (47%)	35 (39%)	51 (57%)	36 (40%)	163 (46%)
Previously used	24 (28%)	26 (29%)	23 (26%)	28 (31%)	101 (28%)
Currently use	22 (25%)	28 (31%)	16 (18%)	25 (28%)	91 (26%)
Alcohol use					
Never used	22 (25%)	19 (21%)	23 (26%)	25 (28%)	89 (25%)
Previously used	5 (6%)	13 (15%)	8 (9%)	14 (16%)	40 (11%)
Currently use	60 (70%)	57 (64%)	59 (66%)	50 (56%)	226 (64%)
Bilateral oophorectomy					
Yes	43 (49%)	47 (53%)	46 (51%)	49 (55%)	185 (52%)
No	44 (51%)	41 (46%)	44 (49%)	40 (45%)	169 (48%)
N/A	0	1 (1%)	0	0	1 (<1%)
Mean BMD (g/cm <sup>2</sup> )	1.05	1.04	1.07	1.04	1.05
Mean yrs since hysterectomy	16.2	15.7	15.5	16.9	16.1

### Patient disposition

355 patients were randomized and received study drug. Table 3 shows the number of patients on study at the scheduled visit times. One hundred ninety six (196) patients (55%) completed the study. The completion rate was highest in the placebo group (67%), at least 13% higher than the completion rates in the Alora dose groups.

Table 3. Patients on study

# patients completing	Placebo	Est .025	Est .05	Est .075	Total
Baseline	87 (100%)	89 (100%)	90 (100%)	89 (100%)	355 (100%)
Cycle 1	85 (98%)	83 (93%)	85(%)	81(91%)	334(94%)
Cycle 2	82 (94%)	82 (92%)	80(%)	79(89%)	323(91%)
Cycle 3	80 (92%)	78(88%)	72(%)	71(80%)	301(85%)
Cycle 5	75 (86%)	70(79%)	68(%)	66(74%)	279(79%)
Cycle 7	70 (80%)	64(72%)	66(%)	63(71%)	263(74%)
Cycle 10	69 (79%)	60(67%)	59(%)	56(63%)	244(69%)
Cycle 13	65 (75%)	55(62%)	56(%)	51(57%)	227(64%)
Cycle 16	61 (70%)	50(56%)	53(%)	47(53%)	211(59%)
Cycle 20	58 (67%)	46(52%)	52(%)	46(52%)	202(57%)
Cycle 23	58 (67%)	45(51%)	50(%)	45(51%)	198(56%)
Cycle 26 (completers)	58 (67%)	44 (49%)	49 (54%)	45 (51%)	196 (55%)
Endpoint	72 (83%)	60 (67%)	64 (71%)	63 (71%)	259 (73%)

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The difference in completion rates between placebo and the Alora dose groups was due primarily to the greater number of dropouts due to adverse reactions, particularly application site reactions (Table 4).

Table 4. Reasons for discontinuation

	Placebo (n=87)	Est .025 (n=89)	Est .05 (n=90)	Est .075 (n=89)	Total (n=355)
AE					
Appl site reaction	0	7	8	9	24
Other	6	7	4	11	28
Inv recommendation	0	1	2	0	3
Prot violations					
Incl criteria	0	0	1	0	1
Excl criteria	1	0	3	0	4
Non-compliance					
Dose schedule	0	9	0	1	1
Visit Schedule	2	4	3	0	9
Excl concom meds	0	1	0	1	2
Voluntary w/d	12	15	13	11	51
Lost to follow-up	8	8	7	11	34
Death	0	2	0	0	2
Total discontinued	29	45	41	44	159

As stated previously, patients dropping prior to Cycle 26 were required by protocol to have a lumbar spine BMD measurement at exit. Table 5 describes the endpoint data. The nature of the endpoint data depended on completion status and, if the patient dropped from the study, time of dropout.

It is important to note that one hundred twenty eight (128) patients dropped prior to their scheduled Cycle 13 visit, but only 32 patients (25% of 128) received exit lumbar spine BMDs as required by protocol. The other 96 patients (75% of 128) did not receive an exit lumbar spine BMD measurement and therefore did not contribute data to an endpoint analysis. Patients dropping after the scheduled Cycle 13 visit all furnished endpoint data, either as exit BMD data or the Cycle 13 BMD measurement.

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Table 5. Description of endpoint data

Patient status	Data used as endpoint	Number of pts (%)	
Completers	Cycle 26 <sup>1</sup>	196 (55%)	
Dropouts	Before Cycle 13	Exit BMD	32 (9%)
		None <sup>2</sup>	96 (27%)
	After Cycle 13	Exit BMD	10 (3%)
		Cycle 13	21 (6%)
Total		355 (100%)	

<sup>1</sup> Three patients completed the study but had no data for Cycle 26. Their Cycle 13 data were used as endpoint data.

<sup>2</sup> These 96 patients (27%) did not contribute data towards an endpoint analysis

The sponsor's ITT population was defined as the set of all randomized subjects with on-treatment data but excluded 14 patients who had vertebral deformities (n=245). This definition was applied to analysis populations which used substantially fewer than 245 patients. For example, several ITT analyses actually consisted of observed cases data. The set of evaluable patients consisted of patients with data who were compliers and did not have major protocol violations.

No single statistical analysis performed by the sponsor used more than 69% of the total number of randomized subjects.

As mentioned above, all of the sponsor's statistical analyses omitted data from 14 patients with vertebral deformities (4, placebo; 3, .025mg; 6, .05mg; 1, .075mg). Vertebral deformities were an exclusion criterion in the protocol: a subject could be excluded from the study if she had "severe fracture deformation that would preclude precise — measurements as determined by the radiographic screening facility". All 14 patients had vertebral deformities at baseline based on x-ray, however, no follow-up (on-treatment) x-rays were performed. In consultation with the medical reviewer, this reviewer excluded from statistical analysis only one of the 14 patients with vertebral deformities. The excluded patient (#14701160) was the only patient with a documented spinal fusion with hardware and had a 116% change in BMD from baseline at endpoint. The statistical results including and excluding the other 13 patients were similar.

Prior to breaking the code, the sponsor changed the statistical analysis from Fisher's LSD to Dunnett's. Of the two multiple comparison procedures, Dunnett's is the preferred procedure since Fisher's LSD does not control the familywise error rate for greater than three treatment groups. The Dunnett's alpha for each of the 3 pairwise comparisons between Alora and placebo is  $\alpha=0.019$ . This alpha level is slightly less conservative than the Bonferroni level  $\alpha=0.017$ . The statistical model was ANOVA with terms for treatment and center.

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Table 6 shows statistical results for the primary endpoint. Figures 1 and 2 show BMD values over time for completers. The aforementioned Patient #14701160 who received .025mg/day was omitted from the graph. For the Cycle 26 endpoint data, all Alora doses were statistically superior to placebo on the primary endpoint.

Table 6. Results for lumbar spine BMD  
ITT dataset (n=258)

	Placebo (n=72)	Est .025 (n=59)	Est .05 (n=64)	Est .075 (n=63)
Baseline mean	1.041	1.054	1.081	1.027
Mean endpoint <sup>1</sup>	1.032	1.069	1.118	1.070
Mean % change from baseline				
Cycle 13 OC <sup>2</sup>	-0.3% (n=65)	1.3% (n=53)	3.5% (n=54)	4.2% (n=50)
Cycle 26 OC <sup>2</sup>	-0.3% (n=56)	1.9% (n=43)	4.1% (n=48)	4.9% (n=45)
Cycle 26 endpoint <sup>1</sup>	-0.8%	1.4%	3.4%	4.2%
Difference vs placebo (cycle 26 endpoint)				
Mean		2.3%	4.2%	5.0%
Least squares mean <sup>3</sup>		2.1%	4.1%	5.0%
p-value <sup>3</sup>		p=.0018 <sup>4</sup>	p=.0001 <sup>4</sup>	p=.0001 <sup>4</sup>

<sup>1</sup> endpoint = last observation carried forward

<sup>2</sup> OC = observed cases. The sponsor did not explicitly include Cycle 26 data in the electronic database. Patients listed as completing the trial and providing exit data were included in the Cycle 26 data.

<sup>3</sup> from ANOVA with treatment and center as factors. Per protocol, sites that had not recruited at least 8 subjects were to be pooled on the basis of geographic region for assessing the treatment-by-center interaction effect. The sponsor combined the 22 centers into 6 pooled centers although there were only 3 small centers (#3913, n=3; #4172, n=5; and #4647, n=2). Since the primary purpose of pooling was to carry out the test of interaction, which was not statistically significant, and there were only 3 centers with fewer than 8 recruited patients, this reviewer considered pooling to be unnecessary. The 'center' term in the model represents the unpooled data.

<sup>4</sup> Statistically significant by Dunnett's test ( $\alpha=0.019$ )

## Missing data

Ninety seven (27%) randomized subjects did not have on treatment data and so did not contribute to the endpoint analysis. This percentage is high but comparable with other data from trials of other estradiols: Climara (24%), Vivelle (30%) and Activella (2 trials; 21% and <20%). Still, the high % of missing data may have impacted the results of the trial. To investigate the sensitivity of the results to missing data, this reviewer performed a type of worst-case analysis similar to one suggested by Dr. Johnson, the medical reviewer for NDA 20-905 (HFD-550, ARAVA for the treatment of active rheumatoid

arthritis), and carried out by the statistical reviewer, Dr. Lu (HFD-720). The statistical approach is formulated to answer the following question: What is the smallest effect size one could impute for the missing data and still retain statistical significance for the all-randomized dataset (n=355)?

The Appendix shows calculations at two Type I error rates,  $\alpha=0.05$  and  $\alpha=0.019$ , comparing the low dose and placebo on the primary endpoint. The more relevant calculation is the one involving  $\alpha=0.019$  since this alpha level accounts for the multiple comparisons with placebo. The mean responses (observed and imputed) for the 2 groups were:

+1.25%	Alora observed
+0.37%	Placebo missing (imputed)
+0.05%	Alora missing (imputed)
-0.83%	Placebo observed

The imputed values in the Alora and placebo missing data cohorts were +0.05% and +0.37, respectively. Therefore, the missing cohort could have a treatment difference as large as -0.32% (the negative sign indicates the treatment difference favors placebo) and still maintain a statistically significant difference between groups. Note that the imputed placebo (Alora) response is closer to the Alora (placebo) observed response than to the placebo (Alora) observed response.

Overall, the results appear to be robust to the missing data.

The procedure could also be carried out for the Alora .05mg and .075mg groups. However, this is unnecessary since the deltas for these groups were larger than the delta for the .025mg group (which has been shown to be robust) and the amount of missing data in the dose groups is similar.

### Covariates

The following covariates were analyzed with respect to their effect on treatment: age, race, previous estrogen use, baseline lumbar spine T score, years since hysterectomy, and BMI. The latter variable was suggested by the FDA Medical reviewer. Graphs 3-8 show boxplots of endpoint BMD data for each treatment group stratified by the covariate of interest. Continuous variables (age, t score, years since hysterectomy and BMI) were stratified by the ~~value~~ value.

The sponsor analyzed subgroups by generating separate p-values for each subgroup. This method is generally inappropriate for examining subgroup differences. This analysis can be misleading when p-values for different subgroups fall above and below .05 giving the impression that the drug works in one subgroup and not in another. This was the case for several subgroups (baseline t score, previous estrogen use, years since hysterectomy)

where the low-dose was judged to be significant in one subgroup but not significant in the other subgroup.

This reviewer analyzed each subgroup using a single statistical model applied to the entire dataset. The model included factors for treatment, subgroup and an interaction term (treatment-by-subgroup) which was evaluated at the 0.10 level of significance. Each dose was compared to placebo in a separate analysis.

This reviewer found three nominally significant interactions with treatment. The interactions were all quantitative in nature. None of these interactions would remain statistically significant at the .10 level if multiplicity from subgroups and doses were taken into account:

- Patients having hysterectomies at least 16-1/2 years prior to trial entry had larger treatment differences (low dose vs placebo) than patients having more recent surgeries (p=.10).
- Patients with high (above median) baseline t scores had greater treatment differences (low dose vs placebo) than patients with lower t scores (p=.085)
- Patients having previously taken estrogen had larger treatment differences (high dose vs placebo) than patients who had not taken estrogen (p=.06)

Input from the FDA medical reviewer is needed to determine how compelling these subgroup differences are from a clinical standpoint.

#### **Fracture data**

Fracture was a safety endpoint. Eleven (11) patients experienced a fracture during the trial, seven in the placebo group and 4 in the combined Alora groups.

#### **Labelling considerations**

1. Treatment effects were about the same for the ITT/endpoint and completer populations. Either present endpoint data in a table, or curves over time for completers. The graph could also show endpoint data separate from the completers.
2. Show by-treatment sample sizes; the label mentions only the overall sample size.
3. The sponsor claims each dose of Alora is effective at all timepoints.

[  Displaying the primary endpoint data over time should be sufficient to give prescribers information about the drug's onset of action. ]

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**Summary and conclusions**

For the ITT dataset, all doses of Alora (.025, .05 and .075mg/day) produced statistically significant changes in lumbar spine BMD compared to placebo at 2 years. These differences were robust with respect to adjustments for multiple comparisons with placebo, and missing data.

J. Todd Sahlroot, Ph.D.  
Mathematical Statistician

Concur: Dr. Nevius

Cc:  
NDA 21-310  
HFD-510/SWu, EColman, PBeaston-Wimmer  
HFD-715/ENevius, TSahlroot  
HFD-700/CAnello

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## APPENDIX

**Question:** What is the smallest effect size one could impute for the missing data and still retain statistical significance for the all-randomized dataset (n=355)? Compare the lowest Alora dose .025mg/day (A) and placebo (P) using the endpoint (lumbar spine % change) data (n=258)

### Methods

Let

- $y_A$  = observed mean response in the Alora group
- $y_P$  = observed mean response in the placebo group
- $n_A$  = total sample size in the Alora group
- $n_P$  = total sample size in the placebo group
- $n_{AO}$  = sample size in the observed Alora cohort
- $n_{PO}$  = sample size in the observed placebo cohort
- $n_{AM}$  = sample size in the missing Alora cohort
- $n_{PM}$  = sample size in the missing placebo cohort
- $y_A - \Delta$  = mean response in the Alora missing group
- $y_P + \Delta$  = mean response in the placebo missing group

where  $\Delta$  is the increment (decrement) in the imputed response for the placebo (Alora) missing cohort with respect to the observed data.

The overall treatment difference  $D(\Delta)$

$$\begin{aligned}
 &= (n_{AO}y_A + n_{AM}(y_A - \Delta)) / n_A - (n_{PO}y_P + n_{PM}(y_P + \Delta)) / n_P \\
 &= (y_A - y_P) - \Delta (n_{AM} / n_A + n_{PM} / n_P)
 \end{aligned}$$

The SE of  $D(\Delta)$  is the usual 2-sample or pooled estimate using the observed SD and the total sample sizes  $n_A$  and  $n_P$ .  $SE(D)$  does not depend on  $\Delta$ .

Calculate  $\Delta$  such that  $Z_{\alpha/2} = D(\Delta) / SE(D)$ .

Solving for  $\Delta$  yields:

$$\Delta = [(y_A - y_P) - Z_{\alpha/2} \cdot SE(D)] / (n_{AM} / n_A + n_{PM} / n_P)$$

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**Results**

	Sample sizes			LS mean <sup>1</sup>	SD <sup>2</sup>
	Observed	Missing	total		
Alora	n <sub>AO</sub> = 59	n <sub>AM</sub> = 30 <sup>3</sup>	n <sub>A</sub> = 89	y <sub>A</sub> = +1.25	SD = 3.86
Placebo	n <sub>PO</sub> = 72	n <sub>PM</sub> = 15	n <sub>P</sub> = 87	y <sub>P</sub> = - 0.83	SD = 4.39

<sup>1</sup>Least square means taken from SAS printout

<sup>2</sup>SD(Alora) = SE(LSM) • sqrt(n<sub>AO</sub>). (SE(LSM) = .5023 taken from SAS printout.)

SD(Placebo) = SE(LSM) • sqrt(n<sub>PO</sub>). (SE(LSM) = .5175 taken from SAS printout.)

<sup>3</sup> One Alora patient with data (endpoint=116%) was coded as missing

$$SE(D) = \text{sqrt} [ (88)(3.86)^2 + 86(4.36)^2 ] / \text{sqrt}(174) \cdot \text{sqrt}(1/89 + 1/87)$$

$$= 0.62$$

$$\Delta = [(1.25 + 0.83) - 1.96 \cdot SE(D)] / [ (89 - 59)/89 + (87 - 72)/87 ]$$

$$= 1.70$$

$$y_A - \Delta = 1.25 - 1.70$$

$$= - 0.45$$

$$y_P + \Delta = -0.83 + 1.70$$

$$= +0.87$$

Therefore, the missing cohort could have a treatment difference as large as D\* satisfying

$$D^* = (y_A - \Delta) - (y_P + \Delta)$$

$$= y_A - y_P - 2\Delta$$

$$= -1.32\% \text{ (favoring placebo)}$$

and still maintain a nominally statistically significant difference between groups (p=.05) for the all-randomized dataset.

To adjust for 3 multiple comparisons with placebo, use a Dunnett's correction ( $\alpha = .019$ ,  $Z_{\alpha/2} = 2.35$ ). Reworking the calculations and replacing 1.96 by 2.35 gives  $\Delta=1.20$  and  $D^* = -0.32$  (favoring placebo).

Figure 1  
mean lumbar spine BMD (g/cm<sup>2</sup>)

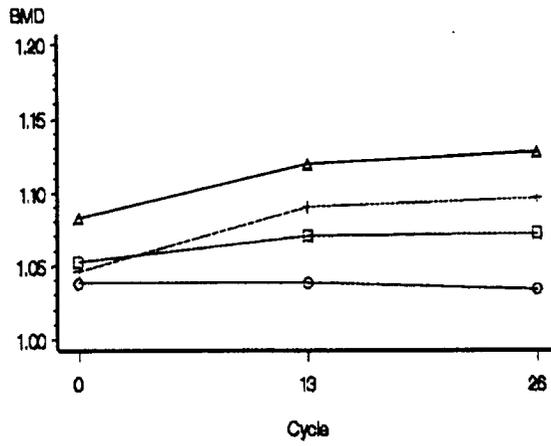


Figure 2  
Lumbar spine BMD  
mean % change from baseline

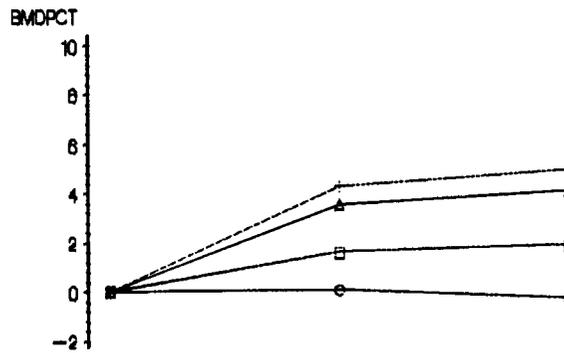
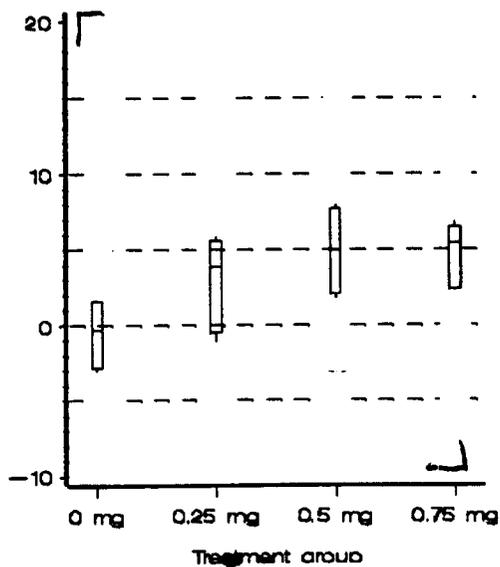
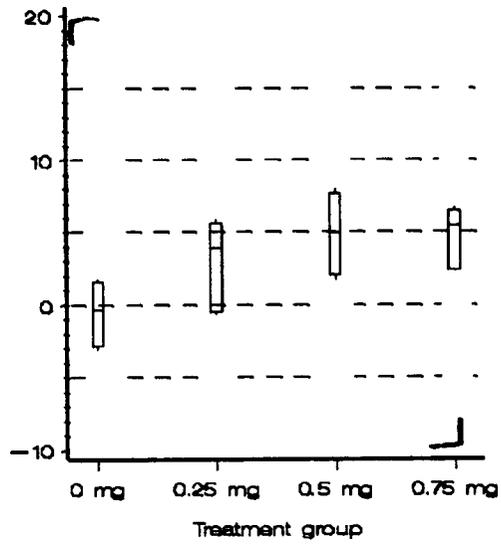


Figure 3  
Trial 1996023  
% change in lumbar spine BMD by age  
AGE= age 55 or older



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Figure 3  
Trial 1998023  
% change in lumbar spine BMD by age  
AGE= age 55 or older



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Figure 4  
% change in lumbar spine BMD by race  
Ethnic code=BLA

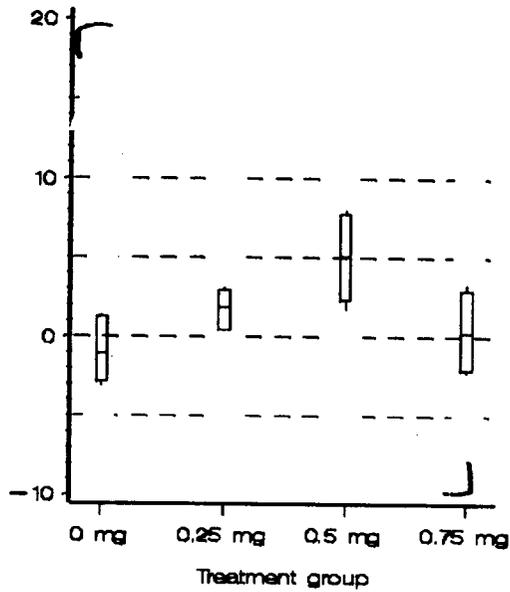
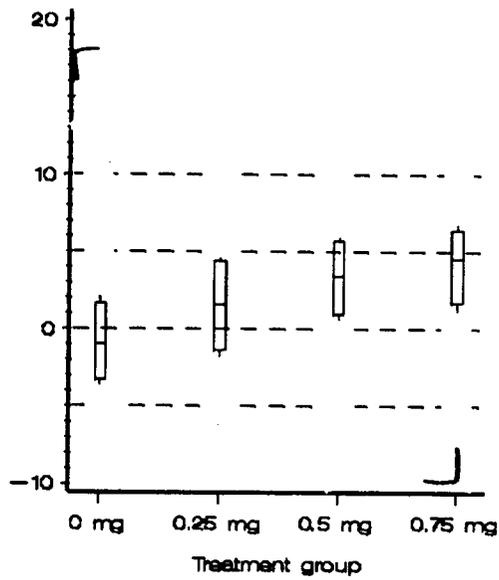
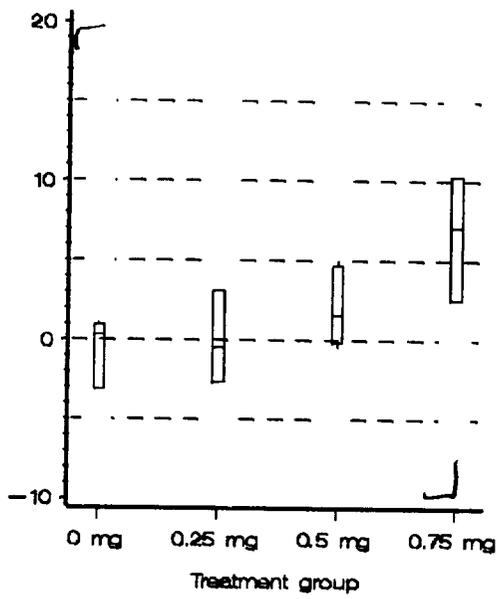


Figure 4  
% change in lumbar spine BMD by race  
Ethnic code=CAUC



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Figure 4  
% change in lumbar spine BMD by race  
Ethnic code=OTHER



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Figure 5  
% change in lumbar spine BMD by estrogen use  
Estrogen use prior= N

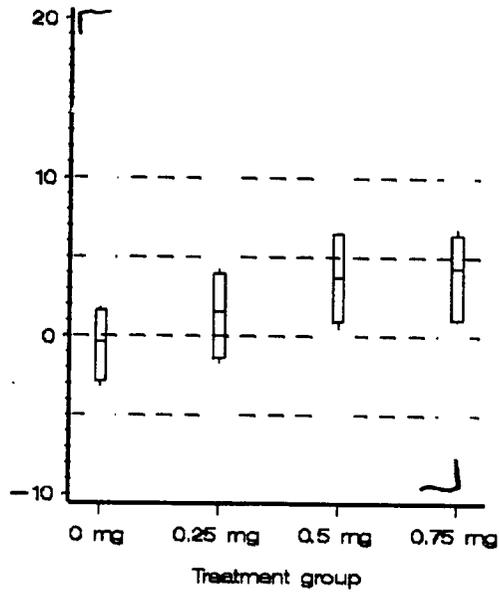
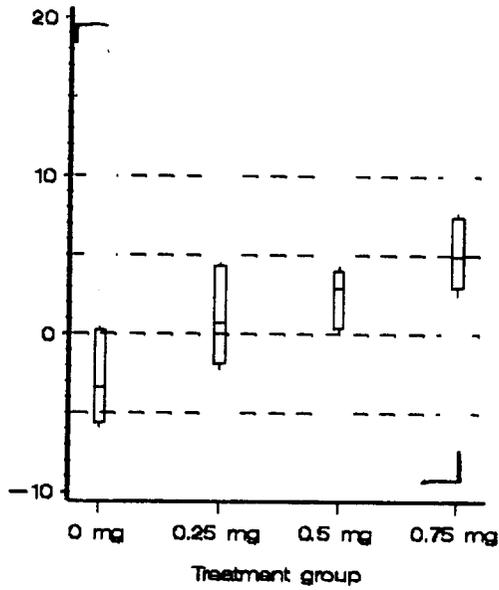


Figure 5  
% change in lumbar spine BMD by estrogen use  
Estrogen use prior= Y



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Figure 6  
 % change in lumbar spine BMD by yrs since hysterectomy  
 HYSTERCT= above median

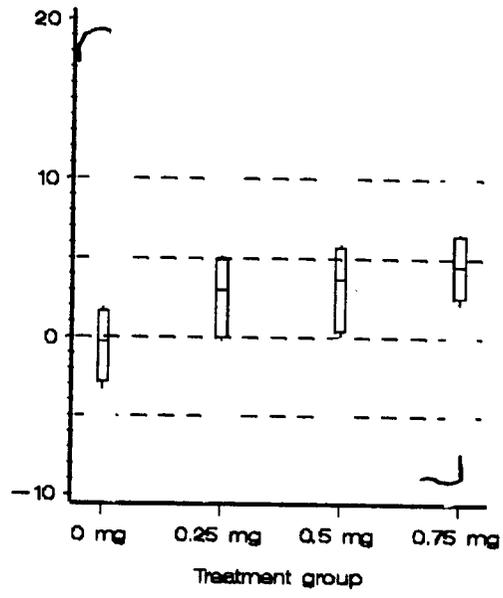
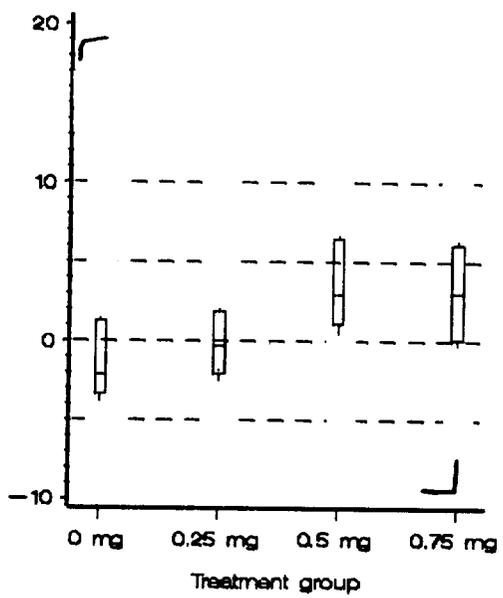


Figure 6  
 % change in lumbar spine BMD by yrs since hysterectomy  
 HYSTERCT= below median



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Figure 7  
% change in lumbar spine BMD by baseline t score  
TSCORE= above median

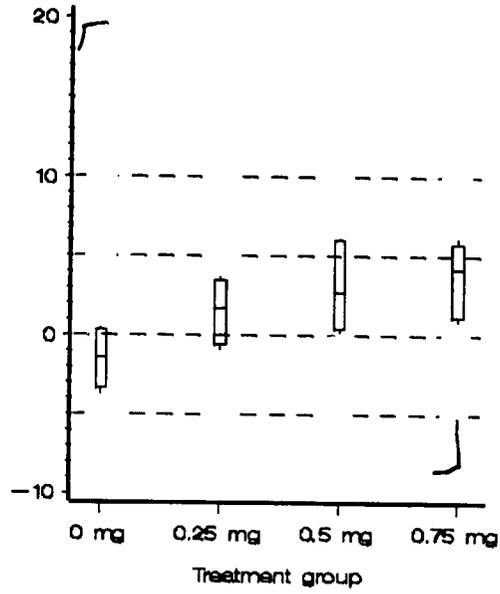
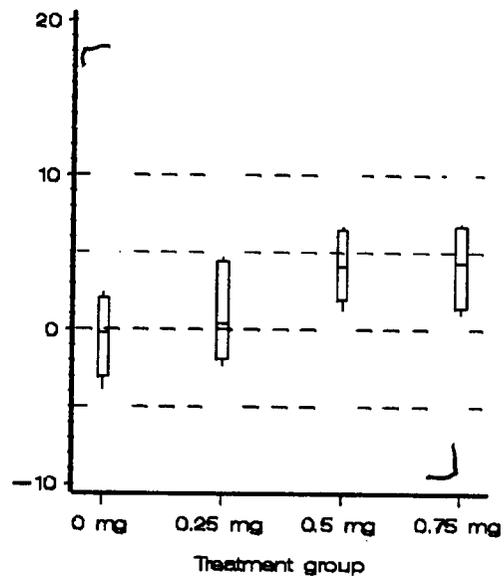


Figure 7  
% change in lumbar spine BMD by baseline t score  
TSCORE= below median



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Figure 8  
% change in lumbar spine BMD by BMI  
BMI = above median

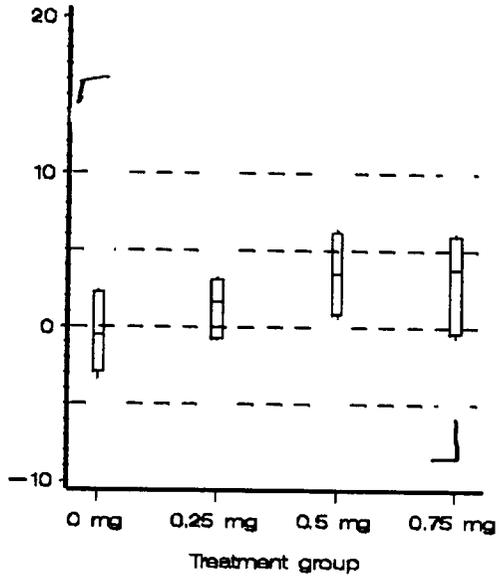
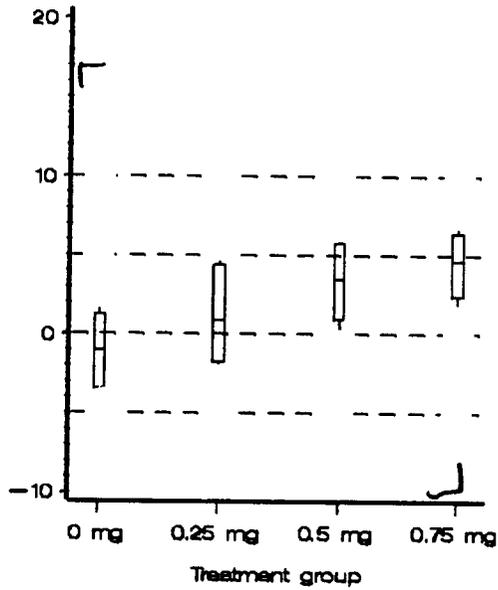


Figure 8  
% change in lumbar spine BMD by BMI  
BMI = below median



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Todd Sahlroot  
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S. Edward Nevius  
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Concur.

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