CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-103

Statistical Review(s)

Statistical Review and Evaluation[1]

APR 6 2000

NDA #: 21-103

Applicant: Novo Nordisk Pharmaceuticals, Inc.

Name of the Drug: Activelle™ (estradiol/norethindrone acetate tablets) 1mg/0.5mg

Indication: Prevention [redacted] of Osteoporosis

Documents Reviewed: Volumes 1.1, 1.2, and Statistical Vols. 1.24 to 1.40, and amendments dated 11-23-99, 12-22-99, 12-23-99

Clinical Reviewer: Joanna Zawadzki, M.D. (HFD-510)

The issues in this review have been discussed with the reviewing medical officer, Joanna Zawadzki, M.D. (HFD-510).

Various Sections of this review are:

I. Background/Introduction

II. Clinical Studies
   1. Study KLIM/PD/11/USA
   2. Study KLIM/PD/4/F

III. Overall Conclusion

I. Background/Introduction

This is an efficacy supplement to Activelle NDA 20-907 application, approved November 18, 1998 by the Division of Reproductive and Urologic Drug Products for the treatment of moderate to severe vasomotor symptoms associated with the menopause, and vulvar and vaginal atrophy, in women with an intact uterus.

Two primary or pivotal studies for efficacy and safety, one domestic and one conducted in France, have been presented. A third Japanese study has been presented as a supportive efficacy and safety study.

[1] Keywords: clinical studies, NDA review

The domestic study KLIM/PD/11/USA was a double-blind, randomized, placebo-controlled study in 17 sites comparing the efficacy and safety of oral tablets of estradiol/norethindrone acetate as well as estradiol alone against placebo in the prevention of osteoporosis in postmenopausal women.

The France study KLIM/PD/4/F was a double-blind, randomized, parallel study in 4 sites comparing the efficacy of two low dose continuous-combined hormone replacement therapies (17β-estradiol 1 mg + NETA 0.25 mg, 17β-estradiol 1 mg + NETA 0.5 mg) and placebo to prevent postmenopausal bone loss.

Summary information of the first two studies, which are reviewed here, is attached as Tables 0.1.1 and 0.1.2[2].

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

1. Study KLIM/PD/11/USA

The Table of some Design, Enrolled Patients, and some other aspects are in the attached Table 0.1.1.

This was a double-blind, randomized, placebo-controlled study in 17 sites (20 investigators) comparing the efficacy and safety of oral tablets of estradiol/norethindrone acetate as well as estradiol alone against placebo in the prevention of osteoporosis in postmenopausal women.

Numbers of patients planned, screened, and randomized were 320, 737, and 327, respectively. Numbers of patients analyzed were: 327 (ITT), 258 (modified ITT), 171 (per-protocol).

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[2] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

1A. Objectives

Original objective was to determine the efficacy and safety of different doses of continuous-combined 17β-estradiol and norethindrone acetate and different doses of estradiol alone compared with placebo in the prevention of osteoporosis in postmenopausal women.

Then the report states, "The between-group comparison of each active treatment therapy and placebo was proposed to be analyzed using Dunnett's test. However, before the treatment codes were unblinded, the focus of the study was determined to be the comparison between the 1mg E_2 + 0.5mg NETA and placebo groups only."

1B. Disposition of Patients

Figure 1.1.1 presents the Percentage of Patients remaining in the study over time. The percents of patients completing the study by treatment group (varied from 44% (1.0mg estradioal) to 67% (2mg E_2 + 1.0 NETA)) and reasons for not completing are in the Table 1.1.2. The adverse event rate in the placebo group (23%) was second to only 1.0mg estradiol alone (35%).

Numbers of patients planned, screened, and randomized were 320, 737, and 327, respectively. Numbers of patients analyzed were: 327 (ITT), 258 (modified ITT), 171 (per-protocol).

There were 410 screen failures. The three most prominent reasons for screen failure were: withdrawal of consent by the subject (21%), unacceptable levels of estradiol (21%), low BMD values (19%).

Seven subjects were ongoing at the time of the study data unblinding (20 May 1998). For efficacy evaluation, only data collected prior to 20 May 1998 were included.

1C. Baseline Comparability of Treatment Groups

The sponsor stated, "Demographic and baseline characteristics for subjects were similar for both treatment groups." None of the baseline comparison p-values provided by the sponsor (submission dated 12-22-99) was significant.

1D. Efficacy Results (Sponsor's Analyses)

The protocol stated, "The primary efficacy variable is BMD of lumbar spine (L1-4), and the secondary efficacy variables are BMD of proximal femur and bone metabolic parameters. BMD will be measured at baseline, 13, and 26 months. … Dunnett's test will be used for the between-group comparison of individual active doses (with or without norethindrone acetate) with placebo. An examination of possible dose response relationship will also be made." The sample size calculation was based on the percent change from baseline of BMD (lumbar spine).

The sponsor states (submission dated 12-22-99), "Before the study was unblinded on May 20, 1999, a revised statistical analysis plan (SAP) was issued …" This SAP, also provided in the same submission, stated, "… The company now determines that 1 mg 17β-estradiol plus 0.5mg norethindrone acetate would be the only continuous combined HRT to be developed for marketing in the US." [Note: By the original Study Report p. 48 or this submission p. 10, the date of unblinding was: May 20, 1998.]

Therefore, the objectives that will be addressed by the statistical analysis in this study were subsequently changed to:

1. Efficacy: to demonstrate that 1 mg 17β-estradiol + 0.5 mg NETA is effective for the prevention of bone loss. …"

By the above statistical analysis plan, month 19 also was included as a BMD measurement time point.

Following are some definitions by this Sponsor in the report (not in the protocol):

ITT: For analysis of safety data, this population included all randomized (327) women.

Modified ITT: For analysis of BMD measurements, this population included all treated women with baseline data and at least one post-randomization BMD measurement (258 patients).

For the Modified Intent-to-Treat (ITT) group, last observation carried forward (LOCF) data, BMD, Change from baseline in BMD, percent change from baseline in BMD and the corresponding p-values are:

Percent Change in Lumbar Spine BMD from Baseline - Last Observation Carried Forward Analysis (page 55 of NDA Volume 1.25)

Treatment	N	Mean	SD	Median	Range	Compared to Placebo P-value	Difference	95 % CI
Placebo	37	-2.12	2.860	-2.06				
[illegible] + 0.25 NETA	37	3.54	3.679	3.64		< 0.001	5.66	(4.18, 7.14)
[illegible] + 0.5 NETA	37	3.80	3.034	3.78		< 0.001	5.92	(4.44, 7.40)
[illegible]	37	0.39	2.927	0.56		0.001	2.51	(1.09, 3.92)
[illegible]	31	2.26	2.760	2.44		< 0.001	4.37	(2.89, 5.86)
[illegible]	37	2.76	2.877	2.95		< 0.001	4.88	(3.46, 6.30)
[illegible] + 1.0 NETA	42	4.99	3.750	4.98		< 0.001	7.11	(5.74, 8.48)

LOCF: Last Observation Carried Forward; P-values are from Analysis of Variance

The box-plots of the changes from baseline for each treatment are attached in the Appendix as Figure 1.3.1. Attached Figure 1.3.2 contains the cumulative distribution curves (provided only for Activelle and placebo) of percent change in lumbar spine BMD from baseline (LOCF). Also attached as Figure 1.3.3 are the graphs for the confidence intervals for the change from baseline for all treatment groups, for the completers, and for months 13, 19, and 26. Note that in the above Table, the confidence intervals are for the difference between each active treatment and placebo (in these differences).

Corresponding Table and a Figure (similar to Figure 1.3.1) for proximal femur neck are attached as Table 1.4.1 and Figure 1.4.2 and those for proximal femur trochanter as Table 1.5.1 and Figure 1.5.2.

From all these results and graphs, covariate analyses, alternative analyses and discussion for robustness, etc. (submission dated 12-22-99), no concern about the efficacy of Activelle is found anywhere, although 2.0mg E_2 + 1.0 NETA was numerically better than Activelle.

1E. <u>Reviewer's Comments and Conclusions on Study KLIM/PD/11/USA</u>

This study provided statistical evidence in favor of the efficacy of Activelle with respect to the primary efficacy variable, the percent

change from baseline of BMD of the **lumbar spine,** and the secondary efficacy variables, the **proximal femur neck** and **the proximal femur trochanter.** Simple alternative analyses (by this reviewer) also provided statistically significant evidence.

2. **Study KLIM/PD/4/F**

The Table of some Design, Enrolled Patients, and some other aspects are in the attached Table 0.1.2.

This was a double-blind, randomized, parallel, placebo-controlled study in 4 centers in France, comparing the efficacy of two low dose continuous-combined hormone replacement therapies (17β-estradiol 1mg + NETA 0.25mg, 17β-estradiol 1mg + NETA 0.5mg) and placebo to prevent postmenopausal bone loss.

Numbers of patients planned, screened, and randomized were 120, 215, and 135, respectively. Numbers of patients analyzed were : 135 (ITT), 73 (per-protocol), 91 (completers).

2A. Objectives

The primary objective was to compare bone mineral density (BMD) in lumbar spine during 2 years of treatment with:

Kliogest Mite A: 1mg 17β-estradiol (E2) and 0.25mg norethisteroneacetate (NETA)

Kliogest Mite B: 1mg 17β-estradiol (E2) and 0.5mg norethisteroneacetate (NETA)

Placebo : No active ingredients

2B. Disposition of Patients

Figure 2.1.1 presents the Percentage of Patients remaining in the study over time. The percents of patients completing the study by treatment group were 65.9% (1.0mg estradioal +0.25mg NETA), 63.0% (1mg E_2 + 0.5 NETA)) and 73.3% (Placebo). The corresponding rates (relative to number randomized) for discontinuation due to adverse events were 25.0%, 28.3%, and 13.3%.

Numbers of patients planned, screened, and randomized were 120,

215, and 135, respectively. Numbers of patients analyzed were: 135 (ITT), 73 (per-protocol), 91 (completers).
The details provided for patient disposition are less for this study than those provided for the other study.

2C. Baseline Comparability of Treatment Groups

The sponsor stated, "Demographic and baseline characteristics for subjects were similar for both treatment groups." None of the baseline comparison p-values provided by the sponsor (submission dated 12-23-99) was significant.

2D. Efficacy Results (Sponsor's Analyses)

The protocol did not mention a primary time-point or visit. The protocol stated, "For each of the three treatment groups and for the measurements at visit 6, 12, 18, and 24 months the % change from baseline of lumbar spine Bone Mineral Density for each patient is calculated."

The amendment dated 12-23-99 stated, "The primary response variable was later changed to "the logarithm of Lumbar Spine BMD at the end of the study (last visit for each subject) divided by BMD at the beginning of the study"."

This change of the original scale to the logarithmic scale is not a concern; this reviewer analyzed the data in the original scale and obtained highly significant p-values with respect to BMD Spine. On request, the sponsor also provided the following in the original scale (12-23-99 amendment):

Percent Change in Lumbar Spine BMD from Baseline

Month	Placebo	Activelle	Treatment Difference	1-Way ANOVA	2-Way ANOVA
6					
N	39	38			
Mean	-0.264	2.717	2.982	<0.001	<0.001
SD	2.981	2.648			
Min-Max					
12					
N	35	32			
Mean	-0.924	4.277	5.201	<0.001	<0.001
SD	3.758	3.704			
Min-Max					
18					
N	35	29			
Mean	-1.114	5.582	6.695	<0.001	<0.001
SD	4.170	4.381			
Min-Max					
24					
N	33	29			
Mean	-1.113	5.934	7.047	<0.001	<0.001
SD	4.257	5.074			
Min-Max					
Last visit					
N	40	38			
Mean	-0.900	5.348	6.249	<0.001	<0.001
SD	4.016	4.843			
Min-Max					

For the Intent-to-Treat (ITT) group, last observation carried forward (LOCF) Last Visit data, the mean difference between Activelle and placebo in percent change from baseline in BMD was 6.249.

The plot of (Mean $\pm$ SEM) of the changes from baseline for each treatment is attached in the Appendix as Figure 2.3.1. Also attached as Figure 2.3.2 is the cumulative distribution curves of percent change in lumbar spine BMD from baseline.

Corresponding Tables and Figures as the above Table and Figure 2.3.1 are attached as Table 2.4.1 and Figure 2.4.2 for proximal femur neck and as Table 2.5.1 and Figure 2.5.2 for proximal femur trochanter.

From the p-values provided on pages 257 onward of volume 1.30, for analyses without as well as with covariates, it is seen that this study provided statistical evidence in favor of the two doses (17β-estradiol 1mg + NETA 0.25mg) and (17β-estradiol 1mg + NETA 0.5mg), with respect to BMD spine (primary), BMD Trochanter (not for the lower dose), BMD Distal Radius, BMD Total Body, and some other variables but not with respect to BMD Femoral Neck and BMD Wards Triangle.

Data on Baseline Dietary Histories and Surgical Menopause were not collected. From the covariate p-values provided (amendment 12-23-99), we can agree with the sponsor's statement, "None of the covariates examined has significant effect on the BMD response."

From all these results and graphs, various analyses (including a non-parametric analysis by this reviewer), and discussion for robustness, etc. (submission dated 12-23-99), no concern about the efficacy of Activelle with respect to the primary efficacy variable is found anywhere.

2E. Reviewer's Comments and Conclusions on Study KLIM/PD/4/F

This study provided statistical evidence in favor of the efficacy of Activelle with respect to the primary efficacy variable, the BMD of the **lumbar spine**, and also with respect to BMD Trochanter (not for the lower dose), BMD Distal Radius, BMD Total Body, and some other variables but not with respect to BMD Femoral Neck and BMD Wards Triangle.

Simple alternative analyses (by this reviewer) also provided statistically significant evidence with respect to % change from baseline of lumbar spine Bone Mineral Density.

From the 95% confidence intervals for individual centers (amendment of 12-23-99), we can agree with the sponsor's statement, "The degree of Activelle protection against bone loss was consistent for all centers."

III. Overall Conclusion

The two studies Study KLIM/PD/11/USA and Study KLIM/PD/4/F provided statistical evidence in favor of the efficacy of Activelle (1.0mg E_2 + 0.50 NETA), although 2.0mg E_2 + 1.0 NETA (present only in the first study) was numerically better than Activelle and 1.0mg E_2 + 0.25 NETA was, generally, not much inferior to Activelle.

In Study KLIM/PD/11/USA, the first measurement was at month 13 and more than 20% patients did not have any measurements and were not included in the efficacy analyses. Based on all the results in the NDA, this reviewer is not too concerned about the efficacy of Activelle. However, sensitivity analyses by imputing the missing patient measurements in alternative ways have been requested of the sponsor. An addendum to this review will be written, if there seems to be any concern.

/S/ 3-28-00

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Mathematical Statistician

Concur: Dr. Sahlroot /S/ 3/28/00

Dr. Nevius /S/ 4/6/00

CC:
Archival NDA 21-103

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This review consists of 10 pages of text and 20 pages of Tables, Figures, etc.

Table 0.1.1

Trial Tabulation - Adequate and Well-controlled Trials - KLIM/PD/11/USA

Ref. Vol.	Study: -investigator(s) -co-ordinating centre -centre(s)	Design	Number of subjects -age -race	Diagnosis + criteria for inclusion	Duration of treatment	Trial product dosage + route of administration	Criteria for evaluation	Results (efficacy)	Results (safety)
	20 investigators and 17 centres in the US	Double-blind, randomised, placebo-controlled **Objectives** To determine the efficacy and safety of different doses of continuous-combined 17β-estradiol (E_2) and norethisterone acetate (NETA) and different doses of E_2 alone compared with placebo in the prevention of osteoporosis in postmenopausal women	327 exposed 189 completed 45-62 yrs Caucasian 301, Black 8, Asian 4, Other 14 *0.25 mg E_2* exp: 45 comp: 25 *0.5 mg E_2* exp: 44 comp: 24 *1 mg E_2* exp: 46 comp: 20 *1 mg E_2 + 0.25 mg NETA* exp: 49 comp: 31 *1 mg E_2 + 0.5 mg NETA* exp: 47 comp: 28 *2 mg E_2 + 1 mg NETA* exp: 48 comp: 32 *placebo* exp: 48 comp: 29	Healthy post-menopausal women with intact uterus, 1-5 years of amenorrhea, 45 years or older, BMD lumbar spine t-score > -2 SD, $E_2 \leq$ 20 pg/mL, FSH ≥ 40 mIU/mL	26 lunar months (lunar month = 28 days)	**Test products** 0.25 mg E_2 0.5 mg E_2 1 mg E_2 1 mg E_2 + 0.25 mg NETA 1 mg E_2 + 0.5 mg NETA 2 mg E_2 + 1 mg NETA 1 tablet daily orally **Reference product** Placebo 1 tablet daily orally **Additional products** Supplemental calcium, 1000 mg daily, was provided for all treatment groups	**Efficacy** *Primary*: Percentage change from baseline in bone mineral density (BMD) at the lumbar spine (L_1-L_4) *Secondary*: Percentage change from baseline in BMD at the hip (femoral neck and femoral trochanter) and biochemical markers of bone turnover (bone-specific alkaline phosphatase, urinary pyridinoline, and urinary deoxy-pyridinoline) **Safety** Adverse events, endometrial histology, physical and gynaecological examination findings, laboratory tests, vital signs	All doses of unopposed E_2 and combinations of E_2 NETA increased BMD at lumbar spine, femoral neck and trochanter compared with placebo. At the end of the trial, the differences in mean percentage change in BMD between 1 mg E_2 + 0.5 mg NETA and placebo were 5.9% at the lumbar spine, 4.1% at the femoral neck, and 5.7% at the trochanter. The addition of 0.25 or 0.5 mg NETA to 1 mg E_2 appeared to enhance the BMD changes at lumbar spine and trochanter compared with 1 mg E_2 unopposed. The percentage of women who gained or maintained BMD with 1 mg E_2, 1 mg E_2 + 0.25 mg NETA, and 1 mg E_2 + 0.5 mg NETA appeared to be similar to that with 2 mg E_2 + 1 mg NETA.	At the end of the trial, endometrial hyperplasia was reported in the placebo (3%), 0.5 mg E_2 (3%), and 1 mg E_2 groups (28%). The number of treatment-emergent adverse events was similar among all groups. The rate of discontinuation due to adverse events was similar among all groups, except the 1 mg E_2 unopposed group where the rate was higher, primarily caused by cases of bleeding and endometrial hyperplasia.

Table 0.1.1 (Repeated in Portrait)

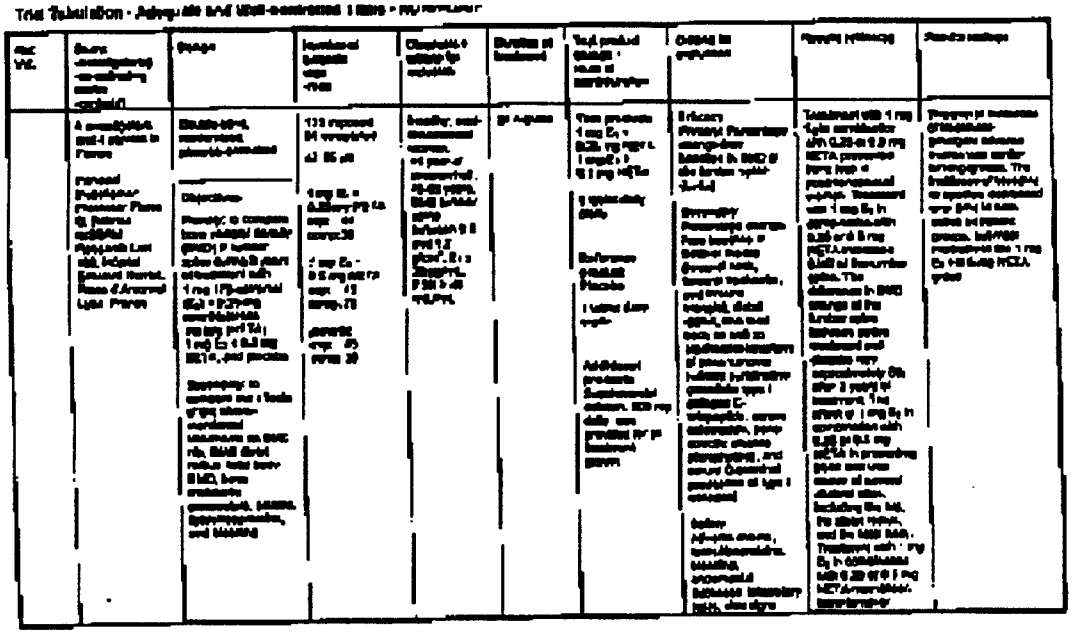

Table 0.1.2

Trial Tabulation - Adequate and Well-controlled Trials - KLIM/PD/4/F

Ref. Vol.	Study: -investigator(s) -co-ordinating centre -centre(s)	Design	Number of subjects -age -race	Diagnosis + criteria for inclusion	Duration of treatment	Trial product dosage + route of administration	Criteria for evaluation	Results (efficacy)	Results (safety)
	4 investigators and 4 centres in France. Principal investigator: Professor Pierre D. Delmas, INSERM Research Unit 403, Hôpital Edouard Herriot, Place d'Arsonval Lyon, France	Double-blind, randomised, placebo-controlled **Objectives** *Primary*: to compare bone mineral density (BMD) in lumbar spine during 2 years of treatment with 1 mg 17β-estradiol (E_2) + 0.25 mg norethisterone acetate (NETA), 1 mg E_2 + 0.5 mg NETA, and placebo *Secondary*: to compare the effects of the above-mentioned treatments on BMD hip, BMD distal radius, total body BMD, bone metabolic parameters, plasma lipids/lipoproteins, and bleeding	135 exposed 91 completed 47-65 yrs *1 mg E_2 + 0.25 mg NETA* exp: 44 comp: 29 *1 mg E_2 + 0.5 mg NETA* exp: 46 comp: 29 *placebo* exp: 45 comp: 33	Healthy, post-menopausal women, >1 year of amenorrhea, 45-65 years, BMD lumbar spine between 0.8 and 1.2 g/cm^2, $E_2 \leq$ 30 pg/mL, FSH > 40 mIU/mL	24 months	**Test products** 1 mg E_2 + 0.25 mg NETA 1 mg E_2 + 0.5 mg NETA 1 tablet daily orally **Reference product** Placebo 1 tablet daily orally **Additional products** Supplemental calcium, 500 mg daily, was provided for all treatment groups	**Efficacy** *Primary*: Percentage change from baseline in BMD at the lumbar spine (L_1-L_4) *Secondary*: Percentage change from baseline in BMD at the hip (femoral neck, femoral trochanter, and Ward's triangle), distal radius, and total body as well as biochemical markers of bone turnover (urinary pyridinoline crosslinks type I collagen C-telopeptide, serum osteocalcin, bone-specific alkaline phosphatase, and serum C-terminal propeptide of type I collagen) **Safety** Adverse events, lipids/lipoproteins, bleeding, endometrial thickness, laboratory tests, vital signs	Treatment with 1 mg E_2 in combination with 0.25 or 0.5 mg NETA prevented bone loss in postmenopausal women. Treatment with 1 mg E_2 in combination with 0.25 or 0.5 mg NETA increased BMD at the lumbar spine. The difference in BMD change at the lumbar spine between active treatment and placebo was approximately 6% after 2 years of treatment. The effect of 1 mg E_2 in combination with 0.25 or 0.5 mg NETA in preventing bone loss was shown at several skeletal sites, including the hip, the distal radius, and the total body. Treatment with 1 mg E_2 in combination with 0.25 or 0.5 mg NETA normalised bone turnover.	The overall incidence of treatment-emergent adverse events was similar among groups. The incidence of bleeding or spotting decreased over time in both active treatment groups, but most markedly in the 1 mg E_2 + 0.5 mg NETA group.

Table 0.1.2 (Repeated in Portrait)

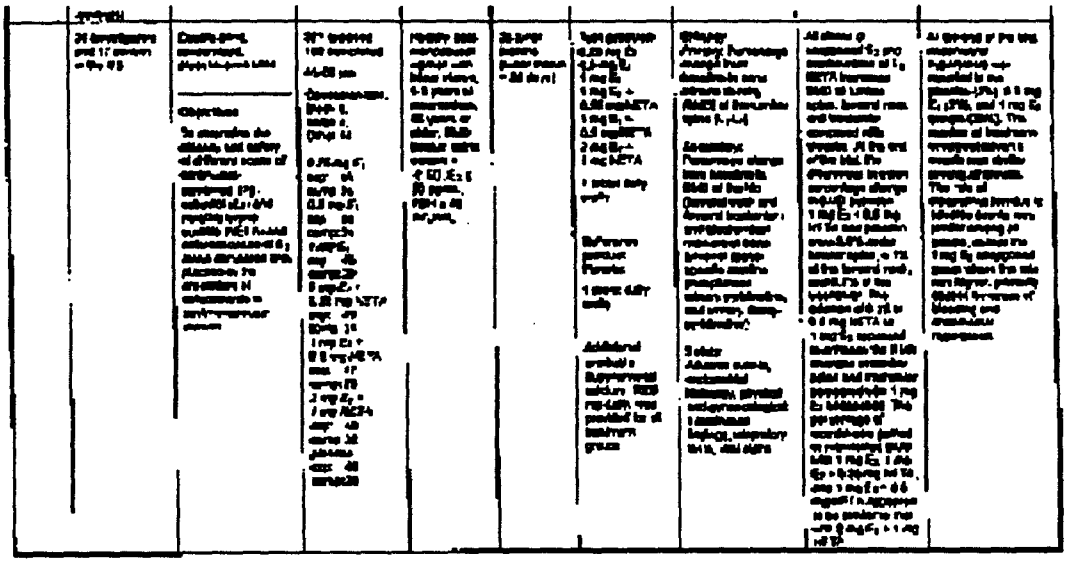

Figure 1.1.1

Subjects Remaining in the Study over Time (page 56 of NDA Volume 1.25)

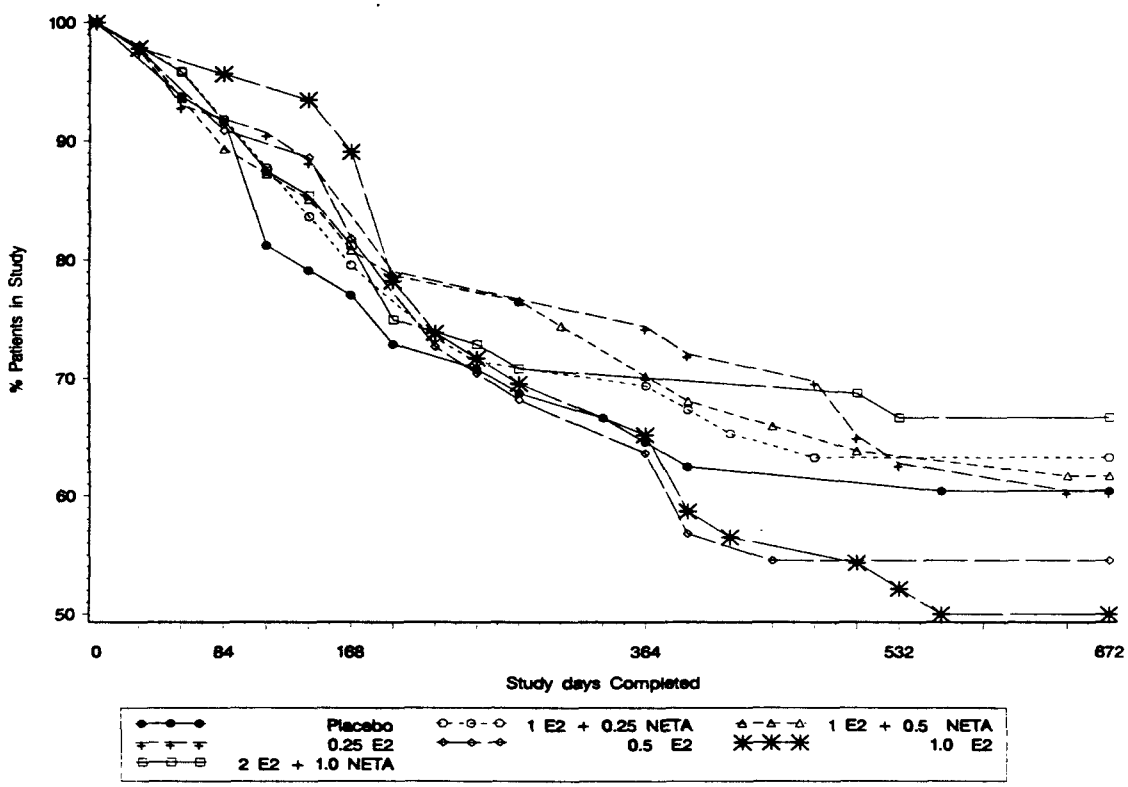

Table 1.1.2

Disposition [N(%)] of Subjects (page 50 of NDA Volume 1.25)

	Placebo	0.25 NETA + E_2	0.5 NETA + E_2	0.25 mg E_2 Alone	0.5 mg E_2 Alone	1.0 mg E_2 Alone	1.0 NETA + E_2
Number treated	48	49	47	45	44	46	48
Discontinued	19 (40)	18 (37)	19 (40)	20 (44)	20 (46)	26 (56)	16 (33)
Completed Study	29 (60)	31 (63)	28 (60)	25 (56)	24 (54)	20 (44)	32 (67)
Reasons for not completing:							
Adverse event	11 (23)	7 (14)	8 (17)	9 (20)	6 (14)	16 (35)	8 (17)
Non-compliance	6 (12)	6 (12)	5 (11)	7 (16)	8 (18)	6 (13)	6 (12)
Other	2 (4)	5 (10)	6 (13)	4 (9)	6 (14)	4 (9)	2 (4)

Figure 1.3.1

Percent Change in Lumbar Spine BMD from Baseline - LOCF

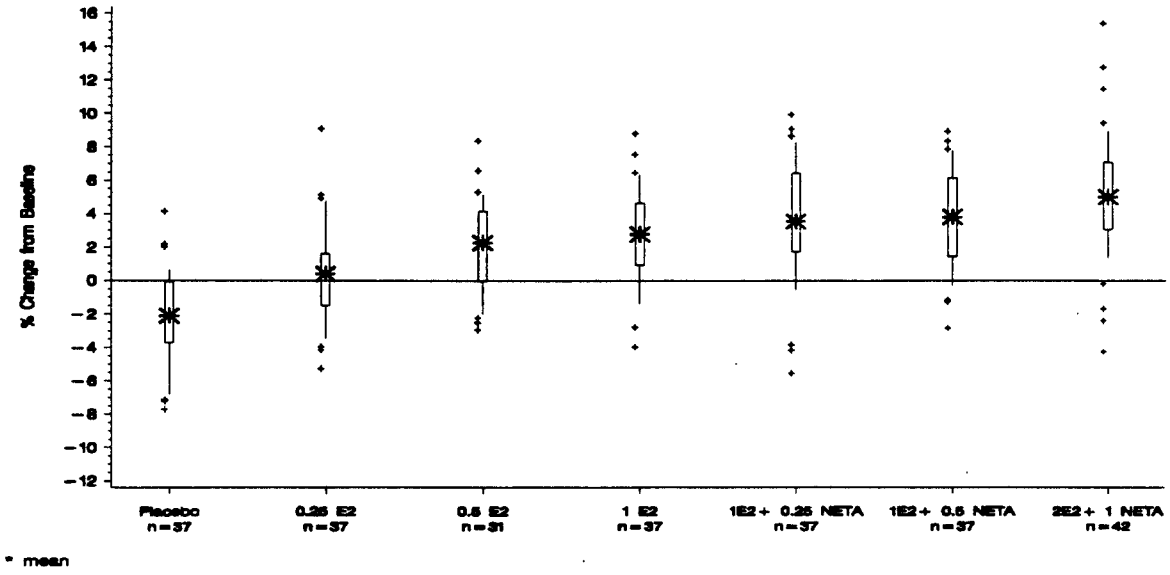

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Figure 1.3.2

Cumulative Distribution Curves of percent change in Lumbar Spine BMD from baseline (LOCF)

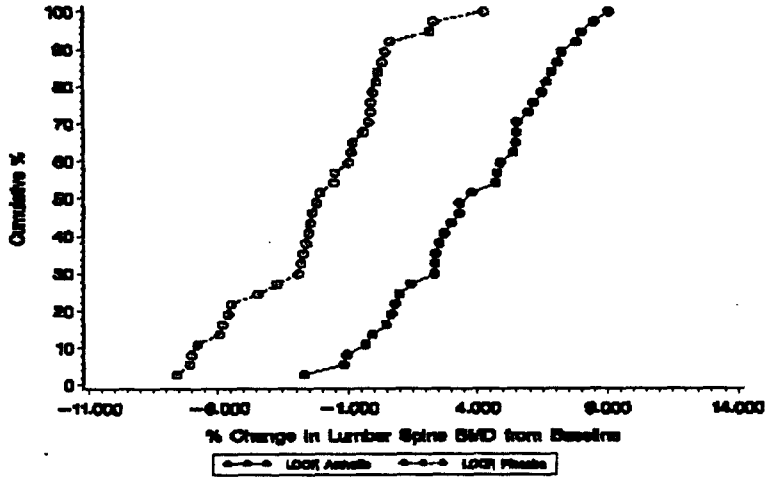

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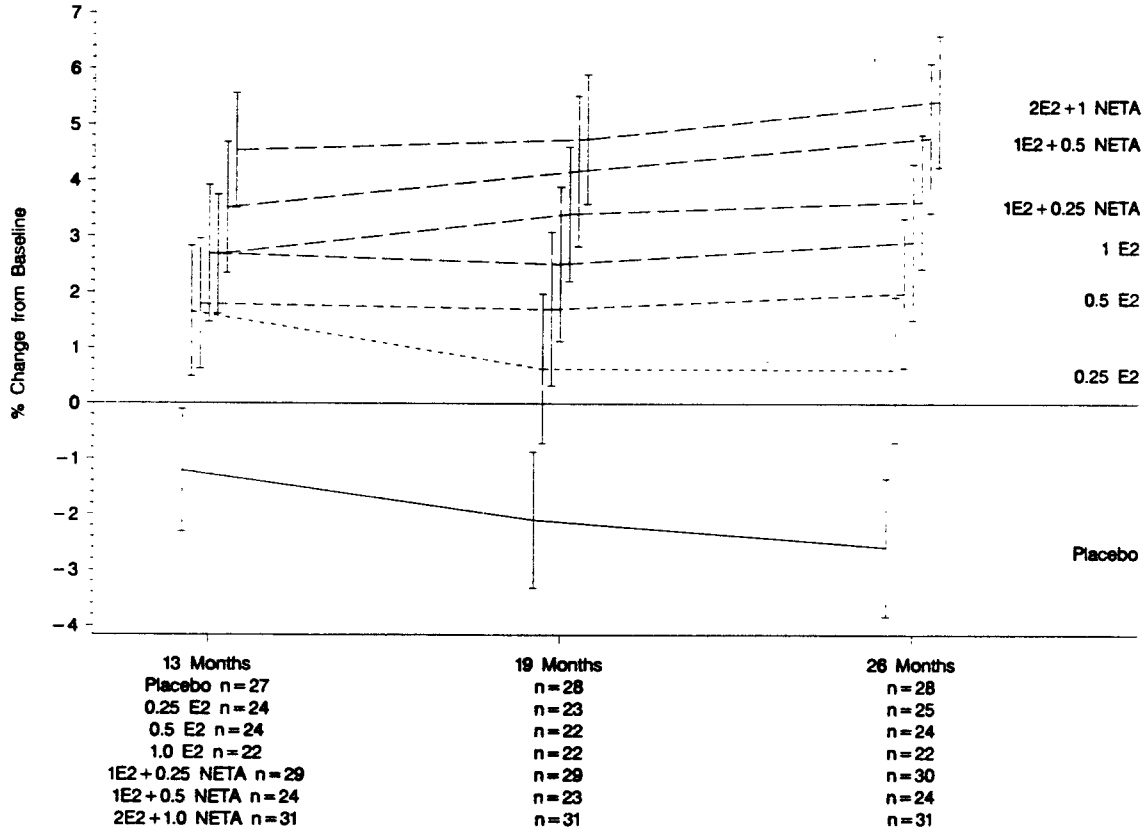
Figure 1.3.3

Percent Change in Lumbar spine BMD from Baseline - Completers

(95% Confidence Intervals)



Mean with 95% confidence interval

APPEARS THIS WAY
ON ORIGINAL

Table 1.4.1

Tables and Figures on Pages 57-59 of NDA Volume 1.25

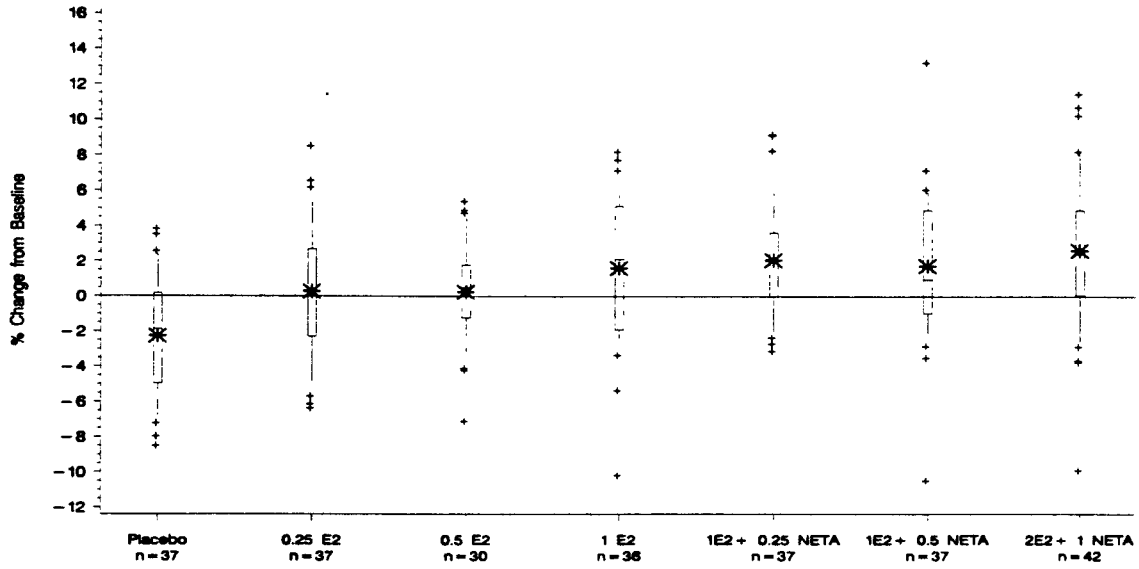
BMD % CHANGE FROM BASELINE -LOCF FOR PROXIMAL FEMUR

Site						Compared to Placebo		
Treatment	N	Mean	SD	Median	Range	P-value	Difference	95 % CI
Femoral neck								
Placebo	37	-2.26	3.418	-1.87				
1 mg E_2 + 0.25 NETA	37	2.09	3.081	1.98		< 0.001	4.35	(2.71, 5.99)
1 mg E_2 + 0.5 NETA	37	1.76	4.101	0.97		12 < 0.001	4.02	(2.38, 5.66)
0.25 mg E_2	37	0.28	3.648	0.43		0.004	2.54	(0.82, 4.27)
0.5 mg E_2	30	0.26	2.864	0.49		0.007	2.52	(0.70, 4.34)
1.0 mg E_2	36	1.63	4.176	2.12		< 0.001	3.89	(2.15, 5.62)
2.0 mg E_2 + 1.0 NETA	42	2.63	4.289	2.40		< 0.001	4.89	(3.21, 6.56)

LOCF: Last Observation Carried Forward
P-values are from Analysis of Variance

APPEARS THIS WAY
ON ORIGINAL

FIGURE 1.4.2. BMD OF FEMORAL NECK: % CHANGE FROM BASELINE -LOCF



* mean

APPEARS THIS WAY
ON ORIGINAL

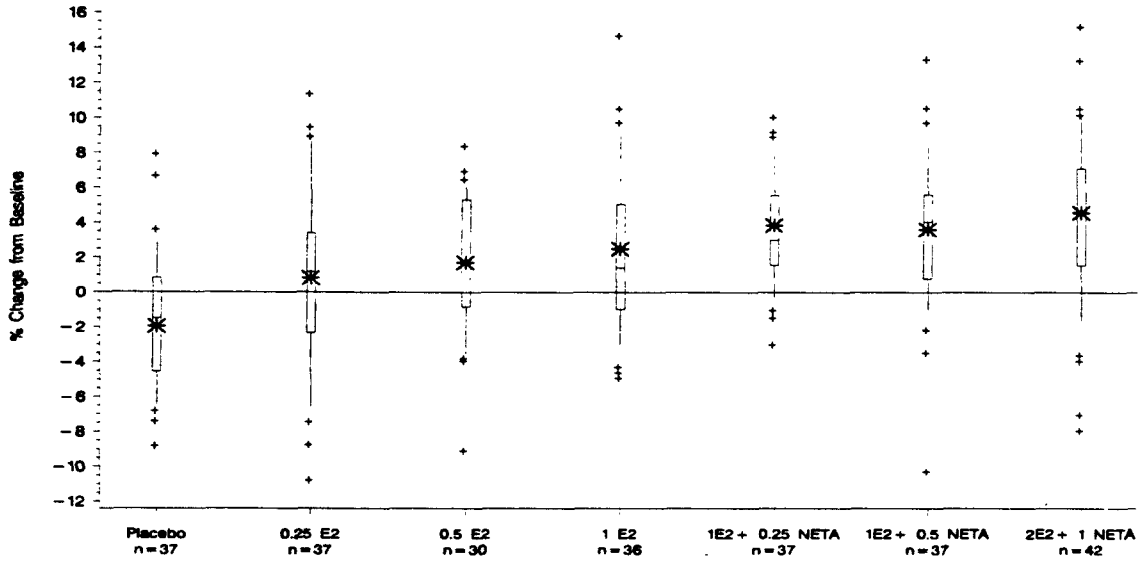
TABLE 1.5.1. BMD % CHANGE FROM BASELINE -LOCF FOR PROXIMAL FEMUR

Site						Compared to Placebo		
Treatment	N	Mean	SD	Median	Range	P-value	Difference	95 % CI
Femoral Trochanter								
Placebo	37	-1.95	4.325	-1.60				
1 mg E_2 + 0.25 NETA	37	3.88	3.714	3.10		< 0.001	5.83	(3.93, 7.74)
1 mg E_2 + 0.5 NETA	37	3.66	4.320	4.10		< 0.001	5.61	(3.70, 7.51)
0.25 mg E_2	37	0.84	5.191	1.17		0.014	2.79	(0.58, 4.99)
0.5 mg E_2	30	1.74	4.115	1.77		0.002	4.48	(2.26, 6.70)
1.0 mg E_2	36	2.53	4.811	1.41		< 0.001	4.48	(2.26, 6.70)
2.0 mg E_2 + 1.0 NETA	42	4.62	5.274	4.60		< 0.001	6.57	(4.43, 8.70)

LOCF: Last Observation Carried Forward
P-values are from Analysis of Variance

APPEARS THIS WAY
ON ORIGINAL

FIGURE 1.5.2. BMD OF FEMORAL TROCHANTER: % CHANGE FROM BASELINE -LOCF



* mean

APPEARS THIS WAY
ON ORIGINAL

Figure 2.1.1

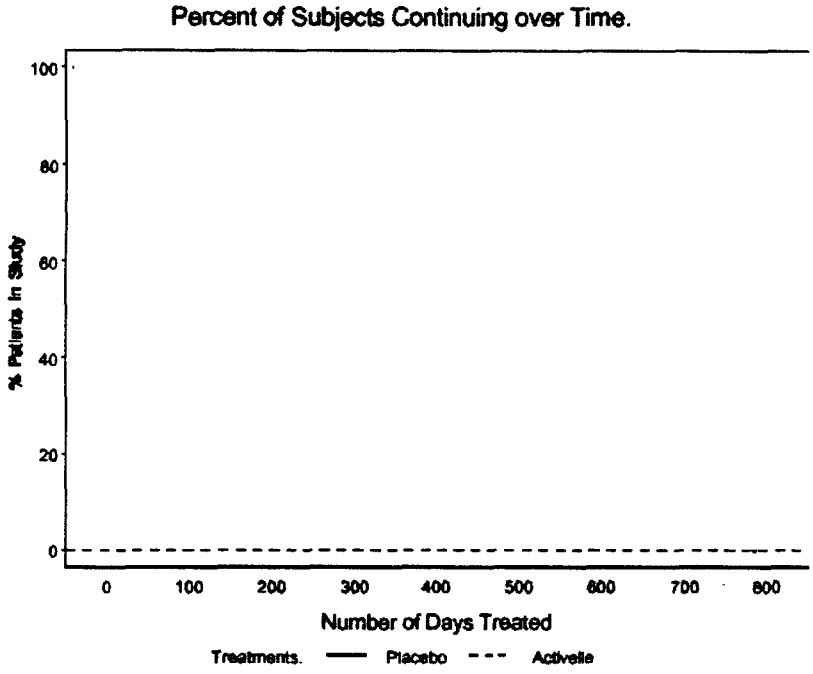


Figure 2.3.1

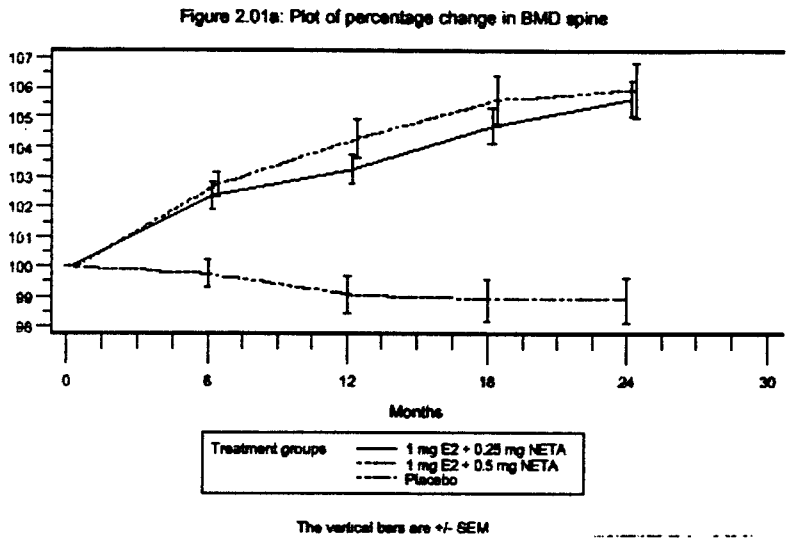


Figure 2.3.2

Cumulative Distribution Curves of Percent Change in Lumbar Spine BMD from baseline (LOCF)

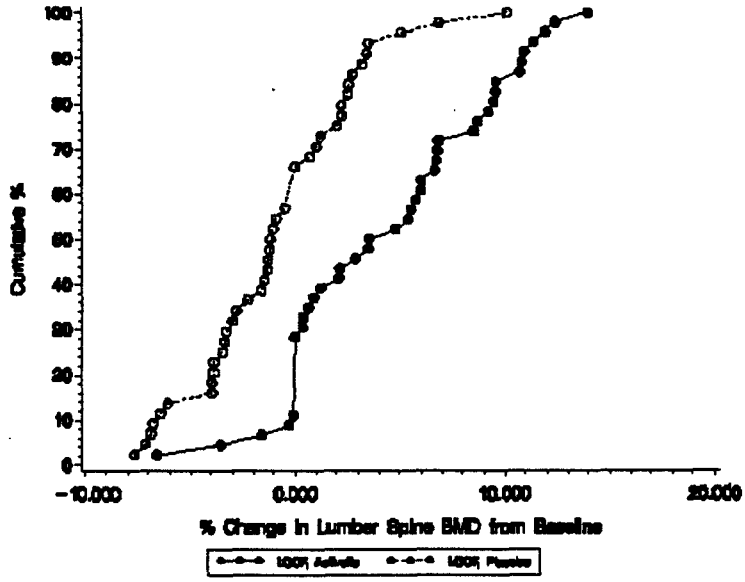


Table 2.4.1
Bone Mineral Density: BMD Femoral Neck (g/cm ∧2).
Percent change from baseline. All randomised patients.

	Placebo	1 mg E2 +0.25 mg NETA	1 mg E2 +0.5 mg NETA
Number of Subjects	45	44	46
Baseline to visit 4 (6 months)			
N	40	36	38
Mean (SD)	-0.16 (4.23)	0.66 (4.93)	0.10 (4.73)
Median	-0.70	0.42	0.32
95% - CI.	[-1.51 - 1.19]	[-1.01 - 2.33]	[-1.45 - 1.66]
Baseline to visit 6 (12 months)			
N	35	32	31
Mean (SD)	-0.62 (4.25)	1.11 (4.49)	1.69 (5.73)
Median	-0.12	0.65	2.26
95% - CI.	[-2.08 - 0.84]	[-0.50 - 2.73]	[-0.41 - 3.79]
Baseline to visit 8 (18 months)			
N	35	28	29
Mean (SD)	-0.62 (6.24)	1.54 (5.51)	1.71 (5.64)
Median	-1.07	2.02	0.96
95% - CI.	[-2.76 - 1.53]	[-0.60 - 3.67]	[-0.44 - 3.85]
Baseline to visit 10 (24 months)			
N	33	28	29
Mean (SD)	-1.19 (4.84)	1.80 (5.78)	0.75 (6.72)
Median	-0.64	1.52	0.27
95% - CI.	[-2.91 - 0.53]	[-0.44 - 4.04]	[-1.81 - 3.30]
Baseline to last visit			
N	40	36	38
Mean (SD)	-1.04 (4.59)	1.48 (5.71)	0.74 (6.13)
Median	-0.78	1.27	0.35
95% - CI.	[-2.51 - 0.43]	[0.46 - 3.41]	[-1.28 - 2.75]

Figure 2.4.2

Plot of percentage change in BMD femoral neck

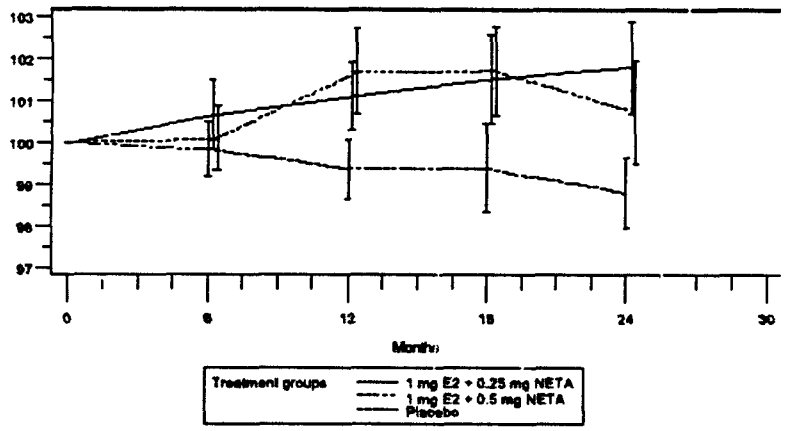


Table 2.5.1
Bone Mineral Density: BMD Trochanter (g/cm ^2).
Percent change from baseline. All randomised patients.

	Placebo	1 mg E2 +0.25 mg NETA	1 mg E2 +0.5 mg NETA
Number of Subjects	45	44	46
Baseline to visit 4 (6 months)			
N	40	36	38
Mean (SD)	0.08 (6.64)	2.79 6.86) (	2.38 6.47) (
Median	-0.24	1.54	2.93
95% - CI.	[-2.04 2.20] -	[0.47 5.11] -	[0.26 - 4.51]
Baseline to visit 6 (12 months)			
N	35	32	31
Mean (SD)	-0.46 (6.89)	2.32 6.79) (	5.72 6.04) (
Median	0.94	2.38	6.35
95% - CI.	[-2.83 1.90] -	[- 4.76] 0.13 -	[3.51 7.94] -
Baseline to visit 8 (18 months)			
N	35	28	29
Mean (SD)	-0.20 (9.91)	2.41 6.07) (	6.58 8.21) (
Median	-0.43	3.67	8.05
95% - CI.	[-3.61 3.20] -	[0.06 4.76] -	[3.46 9.71] -
Baseline to visit 10 (24 months)			
N	33	28	28
Mean (SD)	0.46 (7.16)	4.00 6.47) (	6.60 7.75) (
Median	0.71	3.59	7.56
95% - CI.	[-2.07 3.00] -	[1.50 6.51] -	[3.60 9.61] -
Baseline to last visit			
N	40	36	38
Mean (SD)	0.82 (6.94)	3.34 6.13) (	6.30 7.60) (
Median	0.65	3.28	6.50

Figure 2.5.2

Plot of percentage change in BMD trochanter