

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-001

STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22-001/N-000

Drug Name: Activella® 0.5 mg E₂/0.1 mg NETA

Indication(s): Treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis in women with an intact uterus

Applicant: Novo Nordisk Inc.

Date(s): Received 02/28/06; user fee (10 months) 01/01/07

Review Priority: Standard

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In the EST/PD/4/N+S study, the data have demonstrated that the 1 mg and 2 mg E₂ doses were effective in increasing bone mineral density (BMD) of lumbar spine and hip (femoral neck, trochanter, and Wards triangle) at the end of the 24-month treatment trial. The 0.5 mg E₂ dose, however, resulted in mean and median decreases in lumbar spine BMD from baseline at Month 24. Nevertheless, all 3 doses were better than placebo in preventing bone loss for postmenopausal women with a hysterectomy.

In the KLIM/PD/11/USA study, the data have demonstrated the effectiveness of the 0.5 mg E₂ dose in improving BMD of lumbar spine, femoral neck, and trochanter. In fact, all the treated doses (0.25 mg E₂, 0.5 mg E₂, 1 mg E₂, 1 mg E₂/0.25 mg NETA, 1 mg E₂/0.5 mg NETA, and 2 mg E₂/1 mg NETA) were significantly better than placebo in preventing bone loss for postmenopausal women with an intact uterus. Wards triangle was not evaluated in this trial.

The target population in the proposed labeling is postmenopausal women with an intact uterus. The EST/PD/4/N+S study was conducted in a population including some non-postmenopausal women. Also, all the study subjects had a hysterectomy. In addition, no calcium and/or Vitamin D were supplemented in this European study. All these points make the inclusion of the study to the proposal labeling questionable.

1.2 Brief Overview of Clinical Studies

Novo Nordisk Inc. has submitted an efficacy supplement to NDA 20-907 to the Division of Reproductive and Urologic Products (DRUP) and a full NDA 22-001 to the Division of Metabolic and Endocrine Products (DMEP) requesting approval of lower strength dosage form of Activella[®] (approved on 11/18/1998) for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis, respectively, in women with an intact uterus. Activella[®], the current marketed product, contains 1 mg estradiol (E₂) and 0.5 mg norethindrone acetate (NETA). The lower dosage form will contain 0.5 mg E₂ and 0.1 mg NETA.

The sponsor has submitted the results of 2 old clinical trials (Study Nos. KLIM/PD/11/USA and EST/PD/4/N+S) from the original Activella[®] development program to NDA 22-001. Both studies were Phase III, 2-year, randomized, double-blind, parallel-group, placebo-controlled trials. The former study was conducted at 17 centers in the USA and the latter one was conducted at 1 center in Norway and 1 center in Sweden. The main difference in the inclusion criteria between the 2 studies was that Study KLIM/PD/11/USA recruited subjects who were postmenopausal with an intact uterus, while Study EST/PD/4/N+S recruited

subjects who were either perimenopausal or postmenopausal with a hysterectomy. In addition, calcium 1000 mg was given to patients in the KLIM/PD/11/USA study, while no vitamin supplement was used in the EST/PD/4/N+S study.

The KLIM/PD/11/USA study was reviewed by Dr. Japobrata Choudhury (HFD-715) under NDA 21-103 (stamp date 04/06/2000) for approval of Activella® (1 mg E₂ + 0.5 mg NETA) for prevention and management of osteoporosis. Therefore, the focus of this review was mainly on the EST/PD/4/N+S study.

1.3 Statistical Issues and Findings

In general, there were no serious statistical issues noted by this reviewer for the EST/PD/4/N+S study. As shown in Text Table 1, the 0.5 mg, 1 mg, and 2 mg E₂ doses were all effective in improving BMD of lumbar spine, femoral neck, trochanter, and Wards triangle after 24 months of treatment when compared with the placebo. The significance was particularly evident in the case of lumbar spine BMD (the primary efficacy variable, $p < 0.0005$ for all pair-wise comparisons). However, when compared with baseline, a 0.17% mean (1% in terms of median) reduction in lumbar spine BMD at Month 24 was observed for the 0.5 mg E₂ group. Note that more than 50% of the subjects in the 0.5 mg E₂ group did not respond to the treatment at the end of the 24-month trial (i.e., their change from baseline in lumbar spine BMD at Month 24 was < 0).

Text Table 1 – Study EST/PD/4/N+S: Summary Results for BMD – ITT Population with LOCF

ITT (LOCF)	Raw Mean % Change from Baseline at Month 24 ± SD (N)			
	Lumbar Spine	Femoral Neck	Trochanter	Wards Triangle
Placebo	-3.47 ± 4.22 (36)	-1.96 ± 3.94 (37)	-0.34 ± 5.54 (37)	-2.17 ± 6.46 (37)
0.5 mg E ₂	-0.17 ± 3.28 (37) *	1.76 ± 4.23 (36) *	0.97 ± 5.71 (36)	0.74 ± 6.01 (36)
1.0 mg E ₂	0.84 ± 3.21 (36) *	1.95 ± 4.33 (36) *	3.00 ± 4.88 (36) *	0.71 ± 6.41 (36)
2.0 mg E ₂	1.81 ± 3.21 (37) *	1.87 ± 5.19 (37) *	2.92 ± 4.81 (37) *	1.80 ± 6.84 (37) *

* = Significant at $p \leq 0.05$ when compared with placebo based on Dunnett's t-test

Since the target population was postmenopausal women (defined by baseline FSH > 40 U/L), treatment response of this sub-population alone for the % change from baseline in lumbar spine BMD at Month 24 was evaluated as well. It was found that the treatment differences between the 3 E₂ doses and placebo were more numerically pronounced in the postmenopausal women population than in the whole study population.

Text Table 2 below summarizes the efficacy results for BMD of lumbar spine, femoral neck, and trochanter for the KLIM/PD/11/USA study (copied from the sponsor's Tables 8.2.1.1).

and 8.2.1.2. on pages 55, 57, and 58). According to the sponsor's analysis results, all the treated groups showed a significantly increased mean % change from baseline in lumbar spine, femoral neck, and trochanter BMD at the end of the 24-month trial.

Text Table 2 – Study KLIM/PD/11/USA: Summary Results for BMD – ITT Population with LOCF

ITT (LOCF)	Raw Mean % Change from Baseline at Month 24 ± SD (N)		
	Lumbar Spine	Femoral Neck	Trochanter
Placebo	-2.12 ± 2.86 (37)	-2.26 ± 3.42 (37)	-1.95 ± 4.33 (37)
0.25 mg E ₂	0.39 ± 2.93 (37) *	0.28 ± 3.65 (37) *	0.84 ± 5.19 (37) *
0.5 mg E ₂	2.26 ± 2.76 (31) *	0.26 ± 2.86 (30) *	1.74 ± 4.12 (30) *
1.0 mg E ₂	2.76 ± 2.88 (37) *	1.63 ± 4.18 (36) *	2.53 ± 4.81 (36) *
1.0 mg E ₂ + 0.25 mg NETA	3.54 ± 3.68 (37) *	2.09 ± 3.08 (37) *	3.88 ± 3.71 (37) *
1.0 mg E ₂ + 0.5 mg NETA	3.80 ± 3.03 (37) *	1.76 ± 4.10 (37) *	3.66 ± 4.32 (37) *
2.0 mg E ₂ + 1.0 mg NETA	4.99 ± 3.75 (42) *	2.63 ± 4.29 (42) *	4.62 ± 5.27 (42) *

* = Significant at $p \leq 0.05$ when compared with placebo, using an ANOVA model followed by Dunnett's t-test

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2. INTRODUCTION

2.1 Overview

Activella® (1 mg estradiol + 0.5 mg norethindrone acetate) is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of moderate to severe vulvar and vaginal atrophy associated with menopause, and prevention of postmenopausal osteoporosis (see NDA 20-907 for the first 2 indications and NDA 21-103 for the last one). The current submission to NDA 22-001 is seeking approval of the osteoporosis indication for lower strength dosage form of Activella®, which contains 0.5 mg estradiol (E₂) and 0.1 mg norethindrone acetate (NETA). This new product is intended for once daily oral administration to postmenopausal women with an intact uterus for the treatment of moderate to severe vasomotor symptoms and prevention of postmenopausal osteoporosis. The vasomotor symptom indication, submitted as an efficacy supplement to the original NDA 20-907, is currently reviewed under the Division of Reproductive and Urologic Products (DRUP).

The sponsor has submitted the results of 2 old clinical trials (Study Nos. KLIM/PD/11/USA and EST/PD/4/N+S) from the original Activella® development program to NDA 22-001. Table 1 below shows the studies' highlights. The main difference in the inclusion criteria between the 2 studies was that Study KLIM/PD/11/USA recruited subjects who were postmenopausal with an intact uterus, while Study EST/PD/4/N+S recruited subjects who were either perimenopausal or postmenopausal with a hysterectomy. In addition, calcium 1000 mg was given to patients in the KLIM/PD/11/USA study, while no vitamin supplement was used in the EST/PD/4/N+S study.

The KLIM/PD/11/USA study was reviewed by Dr. Japobrata Choudhury (HFD-715) under NDA 21-103 (stamp date 04/06/2000) for approval of Activella® (1 mg E₂ + 0.5 mg NETA). Therefore, the focus of this review was mainly on the EST/PD/4/N+S study.

2.2 Data Sources

The 2 study reports are located in \\Cdsub1\22001\N_000\2006-02-28\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteo. The electronic data files for the EST/PD/4/N+S study were received on 07/31/2006 and they are located in \\Cdsub1\22001\N_000\2006-07-31\m5\datasets. The derived file, vhl.xpt, has no BMD or biochemical marker data in it. The raw data file, testres.xpt, contains every single data point for all the efficacy variables (at least 37900 records), but no treatment code, last-observation-carried-forward (LOCF) indicator, center information, intention-to-treat (ITT) population indicator, etc. were given. In response to this reviewer's request, 2 concise efficacy files were received on 10/10/2006 via e-mail (also in the EDR \\Cdsub1\22001\N_000\2006-10-12\m5\datasets\ads_fda). However, the quality was still not satisfactory.

Table 1 - Summary of Clinical Studies

Study ID	Number of Study Centers/ Locations	Study start Enrollment status, date	Design Control type	Study drugs, dose, route, regimen	Study objective	# subs by arm	Duration	Gender Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
KLIM/FD/11/USA	17 centres USA	Sept-1995	Randomised, double blind, parallel Placebo	E2 0.25 mg, po, once daily, or	Efficacy and Safety	49/31	26 months	Female	Healthy, postmenopausal women	Percent change from baseline in BMD measurements of the lumbar spine
		Compl. Jul-1996		E2 0.5 mg, po, once daily, or		47/28				
EST/FD/4/N+S	2 centres Norway, Sweden	Nov-1993 Compl. Dec-1997	Randomised, double blind, parallel Placebo	E2 1 mg, po, once daily, or	Efficacy and Safety	45/25	24 months	Female	Hysterectomised, perimenopausal and postmenopausal women	Mean change from baseline in BMD measurements of the lumbar spine
				E2 1 mg + NETA 0.25 mg, po, once daily, or		44/24				
				E2 1 mg + NETA 0.5 mg, po, once daily, or		46/20				
				E2 2 mg + NETA 1 mg, po, once daily, or		48/32				
				Placebo		48/29				
						40/37				
						41/35				
						42/36				
						43/31				

Copied from page 7 of the sponsor's clinical summary report

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints for EST/PD/4/N+S

Study EST/PD/4/N+S was a Phase III, randomized, double-blind, 4-parallel-group, placebo-controlled, 2-center (1 in Norway and 1 in Sweden) trial conducted in peri- and post-menopausal women aged between 44 and 55 years with a hysterectomy. Patients were treated with a once daily oral dose of either 0.5 mg E₂, 1 mg E₂, 2 mg E₂, or placebo for 24 lunar months (1 lunar month = 28 days). Note that the randomization was not stratified by patients' menopausal status (peri or post).

The primary efficacy assessments included bone mineral density (BMD) at the lumbar spine (L₁ – L₄) and hip (femoral neck, trochanter, and Wards triangle) and biochemical bone markers such as serum osteocalcin, serum pyridinium crosslaps, urinary pyridinium crosslaps, urinary hydroxyproline/creatinine, and urinary calcium. They were collected at 0 (baseline), 6, 12, 18, and 24 months. The secondary efficacy assessments were lipids and lipoproteins (only assessed in Norway) and haemostatic parameters (only assessed in Sweden).

3.1.2 Statistical Methods

The primary efficacy endpoint was the logarithm of BMD spine at the end of the study (last visit for each patient) divided by BMD spine at baseline. The sponsor's primary efficacy analysis, as stated in the Statistical Documentation, was based on a normal regression model including the following covariates: serum osteocalcin, serum pyridinium crosslaps, urinary pyridinium crosslaps corrected for creatinine, lumbar spine BMD, body mass index (BMI), and FSH level (≤ 40 U/L or > 40 U/L). In addition, center was also included in the model. Similar analyses were also conducted for BMD at the hip and biochemical bone markers. Note that in the sponsor's clinical study report, time since oophorectomy was also stated as one of the covariates and urinary pyridinium crosslaps itself, not the one corrected for creatinine, was used. This reviewer found that this was not a true statement and it was confirmed by the sponsor.

Since percentage change from baseline was the main efficacy parameter discussed in the proposed labeling and in the KLIM/PD/11/USA study, it was therefore chosen to be the focus of this review. Percentage change from baseline at Month 24 in BMD of lumbar spine and hip were analyzed by this reviewer using the ANCOVA techniques with treatment as the main factor and baseline BMD as the covariate. Dunnett's t-test for simultaneously comparing the 3 E₂ doses with placebo was performed so that the overall Type I error rate for each of the skeletal sites could be preserved. Note that all the pair-wise comparisons and 95% confidence intervals in the sponsor's clinical study report were unadjusted. Similar

analyses were also conducted for biochemical bone markers. The % change from baseline in all the variables mentioned above were also analyzed using the sponsor's model (see the preceding paragraph) as supportive information.

Intention-to-treat (ITT) population, defined as all randomized subjects who received at least 1 dose of trial medication, was the primary efficacy data set. Last-observation-carried-forward (LOCF) approach was used for subjects who withdrew early.

3.1.3 Subject Disposition

A total of 171 subjects were randomized and 166 of them received at least 1 dose of trial medication (123 in Norway and 43 in Sweden): 43, 40, 41, and 42 subjects for the placebo, 0.5 mg E₂, 1 mg E₂, and 2 mg E₂ groups, respectively. The overall withdrawal rate by Month 24 was 16.3% (= 27/166) with the placebo group having the highest dropout rate (see Table 2 below copied from page 62 of the sponsor's report). Adverse event was the most common recorded reason for discontinuation in this trial.

Table 2 – Subject Disposition

	placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Subjects Exposed	43 (100.0%)	40 (100.0%)	41 (100.0%)	42 (100.0%)
Withdrawals	12 (27.9%)	3 (7.5%)	6 (14.6%)	6 (14.3%)
Adverse event	10 (23.3%)	1 (2.5%)	5 (12.2%)	4 (9.5%)
Non-compliance	1 (2.3%)	2 (5.0%)	0 (0.0%)	2 (4.8%)
Ineffective therapy	1 (2.3%)	0 (0.0%)	1 (2.4%)	0 (0.0%)
Intercurrent medical problems	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Completed trial	31 (72.1%)	37 (92.5%)	35 (85.4%)	36 (85.7%)

All the 166 subjects were included in the ITT population.

3.1.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics of all the ITT subjects are shown in Table 3 below (copied from page 65 of the sponsor's report). The overall mean age at entry was 50 years and body mass index (BMI) was around 25 kg/m². All subjects were hysterectomized and the mean time since hysterectomy was about 4 years. In addition, 58 out of the 166 ITT subjects (34.9%) were oophorectomized and 24 of them had a bilateral oophorectomy with baseline FSH > 40 U/L. The numbers of subjects in the placebo, 0.5 mg, 1 mg, and 2 mg groups were 32, 30, 31, and 30, respectively, from the Norwegian center, and 11, 10, 10, and 12, respectively, from the Swedish center. There was no ethnic information recorded in any of the data sets submitted. Based on visual examination, the subjects' demographic and baseline characteristics were similar among the treatment groups.

Table 3 – Demographic and Baseline Characteristics – ITT Population

	placebo	0.5 mg E2	1.0 mg E2	2.0 mg E2
Subjects Exposed	43	40	41	42
Age (yrs)				
N	43	40	41	42
Mean (SD)	49.6 (2.6)	49.9 (2.7)	49.1 (2.3)	49.5 (2.1)
Median	50.0	49.5	49.0	49.0
Min - Max	45.0 - 54.0	44.0 - 55.0	45.0 - 55.0	46.0 - 54.0
Height (cm)				
N	43	40	41	42
Mean (SD)	166.6 (5.5)	168.2 (5.6)	165.7 (5.8)	167.6 (5.9)
Median	168.0	168.0	165.0	167.0
Min - Max	156.0 - 176.0	156.0 - 181.0	155.0 - 180.0	158.0 - 183.0
Weight (kg)				
N	43	40	41	42
Mean (SD)	70.8 (10.0)	69.6 (11.8)	67.8 (11.9)	69.5 (9.2)
Median	71.0	66.0	66.0	68.1
Min - Max	51.0 - 99.0	46.0 - 96.0	49.0 - 100.0	52.0 - 98.0
BMI (kg/m ²)				
N	43	40	41	42
Mean (SD)	25.6 (3.8)	24.5 (3.4)	24.7 (4.0)	24.7 (3.1)
Median	24.8	23.7	23.8	24.3
Min - Max	18.7 - 37.6	17.7 - 31.2	18.0 - 35.8	19.8 - 33.1
Oophorectomy				
Yes	11 (25.6%)	14 (35.0%)	16 (39.0%)	17 (40.5%)
Lateral	5 (11.6%)	9 (22.5%)	7 (17.1%)	13 (31.0%)
Bilateral	6 (14.0%)	5 (12.5%)	9 (22.0%)	4 (9.5%)
No	32 (74.4%)	26 (65.0%)	24 (58.5%)	25 (59.5%)
Age at oophorectomy (yrs)				
N	11	14	16	17
Mean (SD)	48.0 (3.2)	46.2 (3.4)	44.6 (5.5)	42.1 (9.2)
Median	48.0	46.0	46.0	45.0
Min - Max	43.0 - 53.0	40.0 - 51.0	30.0 - 50.0	21.0 - 50.0
Time since oophorectomy (yrs)				
N	11	14	16	17
Mean (SD)	2.3 (1.3)	4.3 (3.4)	4.8 (6.6)	7.5 (9.6)
Median	2.0	3.0	2.0	3.0
Min - Max	0.0 - 4.0	0.0 - 11.0	0.0 - 24.0	0.0 - 32.0
Age at hysterectomy (yrs)				
N	43	40	41	42
Mean (SD)	45.1 (4.6)	45.4 (3.9)	45.8 (3.1)	44.9 (4.6)
Median	46.0	46.0	46.0	46.0
Min - Max	33.0 - 53.0	33.0 - 51.0	39.0 - 52.0	32.0 - 52.0
Time since hysterectomy (yrs)				
N	43	40	41	42
Mean (SD)	4.4 (4.0)	4.4 (3.8)	3.4 (3.2)	4.5 (4.8)
Median	3.0	3.0	2.0	3.0
Min - Max	0.0 - 19.0	0.0 - 16.0	0.0 - 14.0	0.0 - 19.0
Systolic blood pressure (mmHg)				
N	43	40	41	42
Mean (SD)	122.9 (11.4)	121.7 (14.4)	122.1 (15.8)	119.1 (14.8)
Median	120.0	120.0	120.0	120.0
Min - Max	100.0 - 150.0	100.0 - 150.0	95.0 - 160.0	90.0 - 140.0
Diastolic blood pressure (mmHg)				
N	43	40	41	42
Mean (SD)	80.2 (5.9)	78.3 (8.5)	78.8 (7.1)	77.4 (10.9)
Median	80.0	80.0	80.0	80.0
Min - Max	70.0 - 90.0	60.0 - 90.0	60.0 - 90.0	50.0 - 90.0

As Table 4 shows, of the 166 ITT subjects, 26 of them (15.7%) had a baseline FSH \leq 20 U/L at entry which was a violation of inclusion criterion, and 28 of them (16.9%) had a baseline FSH between 20 and up to 40 U/L which was defined as perimenopausal by the sponsor.

Table 4 – Menopausal Status – ITT Population

FSH	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂	Total
\leq 20 U/L (exclusion criterion)	7	5	8	6	26 (15.7%)
> 20 U/L and \leq 40 U/L (perimenopausal)	11	2	8	7	28 (16.9%)
> 40 U/L (postmenopausal)	25	33	25	29	112 (67.5%)

3.1.5 Efficacy Results and Discussion

The following statistical analyses were based on this reviewer's model using treatment as the main factor and baseline as the covariate. The % change from baseline in BMD at Month 24 analyzed using the sponsor's model generated similar results. Also, this reviewer's findings based on the % change from baseline in BMD generally agree with the sponsor's results based on the logarithm of the ratio (last visit/baseline), unless otherwise stated.

BMD of Lumbar Spine (L1-L4). After 2 years of treatment, the 1 mg and 2 mg E₂ groups showed an increased mean lumbar spine BMD over baseline, while the placebo and 0.5 mg E₂ group showed a decrease (Table 5). The % changes from baseline in each study group were normally distributed based on the Shapiro-Wilk normality test ($p > 0.10$). The raw mean % changes from baseline for the placebo, 0.5 mg, 1 mg, and 2 mg groups were -3.47%, -0.17%, 0.84%, and 1.81%, respectively. Note that in terms of median, the 0.5 mg group actually exhibited a ~1% reduction from baseline. In addition, according to the 95% confidence intervals, the lumbar spine BMD at Month 24 in the 0.5 mg and 1 mg groups could be reduced from baseline by as much as 1.3% and 0.2%, respectively.

Nevertheless, according to Dunnett's t-test, the mean % changes from baseline in lumbar spine BMD in all the 3 E₂ groups were significantly better than that in the placebo group at the end of the trial ($p < 0.0005$ for all pair-wise comparisons). Wilcoxon-Mann-Whitney test (a non-parametric test) also showed significant group comparisons at $p < 0.005$. The treatment effect was in a positive dose-response fashion.

Table 5 – Results for Lumbar Spine BMD – ITT Population with LOCF

	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Raw mean lumbar spine BMD \pm standard deviation (sample size)				
Month 0	1.20 \pm 0.17 (36)	1.10 \pm 0.13 (37)	1.15 \pm 0.13 (36)	1.15 \pm 0.14 (37)
Month 24	1.16 \pm 0.18 (36)	1.09 \pm 0.13 (37)	1.16 \pm 0.14 (36)	1.17 \pm 0.15 (37)

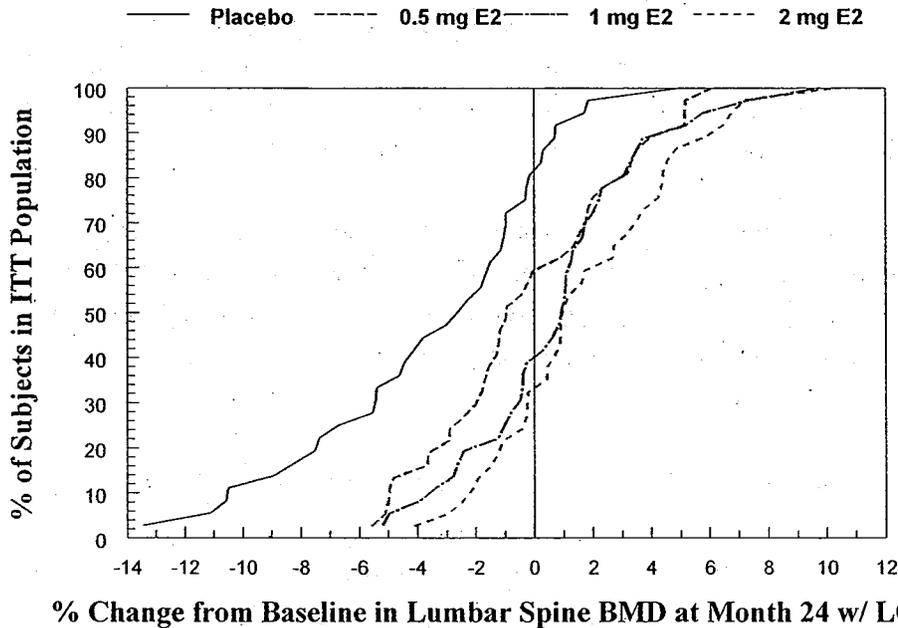
Raw mean % change from baseline ± standard deviation (sample size)				
Month 24	-3.47 ± 4.22 (36)	-0.17 ± 3.28 (37)	0.84 ± 3.21 (36)	1.81 ± 3.21 (37)
	Median = -2.47	Median = -0.93	Median = 0.98	Median = 1.03
	95% CI (-4.9, -2.0)	95% CI (-1.3, 0.9)	95% CI (-0.2, 1.9)	95% CI (0.7, 2.9)
Least-squares mean % change from baseline ± standard error (sample size)				
Month 24	-3.57 ± 0.59 (36)	-0.06 ± 0.59 (37)	0.84 ± 0.58 (36)	1.80 ± 0.58 (37)
Comparison against Placebo				
Treatment Difference		3.51	4.41	5.37
Dunnett's p-value		0.0002	<0.0001	<0.0001
Dunnett's 95% CI		(1.50, 5.51)	(2.44, 6.38)	(3.41, 7.33)

Wilcoxon-Mann-Whitney test (non-parametric test) also showed significant group comparisons at p < 0.005.

As depicted in Figure 1, 61% and 68% of the subjects in the 1 mg and 2 mg groups, respectively, responded to the treatment at the end of the 24-month trial (change from baseline in lumbar spine BMD at Month 24 ≥ 0). However, only 19% and 41% of the subjects in the placebo and 0.5 mg groups had such findings. Note that one can easily obtain the % of subjects achieving a given level of response for any definition of responders.

Figure 1

Study EST/PD/4/N+S: Cumulative Distribution Function
% of subjects having at most % change in lumbar spine BMD



BMD of Femoral Neck. After 2 years of treatment, all the E₂ groups showed an increased mean femoral neck BMD over baseline, while the placebo group showed a decrease (Table 6). The raw mean % changes from baseline for the placebo, 0.5 mg, 1 mg, and 2 mg groups were -1.96%, 1.76%, 1.95%, and 1.87%, respectively. The 3 E₂ groups were all significantly better than the placebo group in improving femoral neck BMD at the end of the 24-month trial ($p < 0.01$ for all pair-wise comparisons).

Table 6 – Results for Femoral Neck BMD – ITT Population with LOCF

	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Raw mean femoral neck BMD ± standard deviation (sample size)				
Month 0	0.94 ± 0.12 (37)	0.92 ± 0.12 (36)	0.91 ± 0.09 (36)	0.90 ± 0.13 (37)
Month 24	0.92 ± 0.12 (37)	0.94 ± 0.13 (36)	0.93 ± 0.09 (36)	0.91 ± 0.12 (37)
Raw mean % change from baseline ± standard deviation (sample size)				
Month 24	-1.96 ± 3.94 (37) Median = -1.31 95% CI (-3.3, -0.6)	1.76 ± 4.23 (36) Median = 1.06 95% CI (0.3, 3.2)	1.95 ± 4.33 (36) Median = 2.33 95% CI (0.5, 3.4)	1.87 ± 5.19 (37) Median = 1.65 95% CI (0.1, 3.6)
Least-squares mean % change from baseline ± standard error (sample size)				
Month 24	-1.79 ± 0.72 (37)	1.78 ± 0.73 (36)	1.91 ± 0.73 (36)	1.72 ± 0.72 (37)
Comparison against Placebo				
Treatment Difference		3.57	3.70	3.51
Dunnett's p-value		0.0020	0.0013	0.0023
Dunnett's 95% CI		(1.13, 6.00)	(1.26, 6.15)	(1.08, 5.95)

BMD of Trochanter. After 2 years of treatment, all the E₂ groups showed an increased mean trochanter BMD over baseline, while the placebo group showed a decrease (Table 7). The raw mean % changes from baseline for the placebo, 0.5 mg, 1 mg, and 2 mg groups were -0.34%, 0.97%, 3.00%, and 2.92%, respectively. Note that the trochanter BMD at Month 24 in the 0.5 mg group could actually be reduced from baseline by as much as 1% according to the 95% confidence interval.

When compared with the placebo, the 1 mg and 2 mg doses, but not the 0.5 mg one, were significantly better in improving trochanter BMD at the end of the 24-month trial ($p < 0.05$ for both pair-wise comparisons).

Table 7 – Results for Trochanter BMD – ITT Population with LOCF

	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Raw mean trochanter BMD ± standard deviation (sample size)				

Month 0	0.80 ± 0.13 (37)	0.78 ± 0.12 (36)	0.78 ± 0.11 (36)	0.79 ± 0.12 (37)
Month 24	0.80 ± 0.14 (37)	0.79 ± 0.12 (36)	0.80 ± 0.10 (36)	0.81 ± 0.12 (37)
Raw mean % change from baseline ± standard deviation (sample size)				
Month 24	-0.34 ± 5.54 (37) Median = -1.78 95% CI (-2.2, 1.5)	0.97 ± 5.71 (36) Median = 0.76 95% CI (-1.0, 2.9)	3.00 ± 4.88 (36) Median = 2.33 95% CI (1.4, 4.7)	2.92 ± 4.81 (37) Median = 2.84 95% CI (1.3, 4.5)
Least-squares mean % change from baseline ± standard error (sample size)				
Month 24	-0.25 ± 0.86 (37)	0.93 ± 0.87 (36)	2.96 ± 0.87 (36)	2.92 ± 0.86 (37)
Comparison against Placebo				
Treatment Difference		1.18	3.22	3.18
Dunnett's p-value		0.6497	0.0258	0.0266
Dunnett's 95% CI		(-1.72, 4.09)	(0.31, 6.12)	(0.30, 6.06)

BMD of Wards Triangle. After 2 years of treatment, all the E₂ groups showed an increased mean Wards triangle BMD over baseline, while the placebo group showed a decrease (Table 8). The raw mean % changes from baseline for the placebo, 0.5 mg, 1 mg, and 2 mg groups were -2.17%, 0.74%, 0.71%, and 1.80%, respectively. Note that in terms of median, the 0.5 mg group actually exhibited a ~1% reduction from baseline. In addition, according to the 95% confidence intervals, the Wards triangle BMD at Month 24 in the 0.5 mg, 1 mg, and 2 mg groups could be reduced from baseline by as much as 1.3%, 1.5%, and 0.5%, respectively.

The 2 mg group was significantly better than the placebo group in improving Wards triangle BMD at the end of the 24-month trial ($p < 0.05$). No such significant findings were observed for the 0.5 mg and 1 mg groups.

Table 8 – Results for Wards Triangle BMD – ITT Population with LOCF

	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Raw mean Wards triangle BMD ± standard deviation (sample size)				
Month 0	0.81 ± 0.13 (37)	0.81 ± 0.14 (36)	0.80 ± 0.11 (36)	0.78 ± 0.13 (37)
Month 24	0.79 ± 0.13 (37)	0.81 ± 0.15 (36)	0.81 ± 0.11 (36)	0.79 ± 0.14 (37)
Raw mean % change from baseline ± standard deviation (sample size)				
Month 24	-2.17 ± 6.46 (37) Median = -2.74 95% CI (-4.3, -0.0)	0.74 ± 6.01 (36) Median = -0.80 95% CI (-1.3, 2.8)	0.71 ± 6.41 (36) Median = 0.64 95% CI (-1.5, 2.9)	1.80 ± 6.84 (37) Median = 1.88 95% CI (-0.5, 4.1)
Least-squares mean % change from baseline ± standard error (sample size)				
Month 24	-2.10 ± 1.06 (37)	0.79 ± 1.07 (36)	0.72 ± 1.07 (36)	1.67 ± 1.06 (37)

Comparison against Placebo				
Treatment Difference		2.89	2.82	3.77
Dunnett's p-value		0.1401	0.1531	0.0348
Dunnett's 95% CI		(-0.68, 6.46)	(-0.74, 6.39)	(0.21, 7.33)

Note that the 0.5 mg and 1 mg E₂ groups were claimed to be significantly better than the placebo group in the sponsor's analysis with covariates (see Appendix I). However, if their p-values had been adjusted using either Dunnett or Bonferroni's method, they would have not shown any statistical significance.

Biochemical Bone Markers. After 2 years of treatment, the means and medians of the biochemical bone markers of interest were decreased over baseline in all the E₂ groups, but were increased in the placebo group (Table 9). According to Dunnett's t-test, all the 3 E₂ groups were significantly better than the placebo group in decreasing serum osteocalcin, serum pyridinium crosslaps, and urinary pyridinium crosslaps corrected for creatinine at the end of the 24-month trial ($p < 0.001$ for all cases). The significant findings were not consistently seen among the 3 E₂ groups in the cases of urinary hydroxyproline/creatinine and urinary calcium. Specifically, no significant findings were observed in the urinary hydroxyproline/creatinine and only the 2 mg dose showed non-significance when compared with the placebo in urinary calcium.

Table 9 – Raw Mean % Change from Baseline at Month 24 ± SD (N) for Biochemical Bone Markers

ITT (LOCF)	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Serum Osteocalcin	16.6 ± 32.2 (38) Median = 8.8	-19.4 ± 22.8 (40) Median = -22.2	-17.4 ± 23.2 (38) Median = -19.7	-24.4 ± 22.4 (37) Median = -28.4
Serum Pyridinium Crosslaps	21.2 ± 48.0 (38) Median = 16.4	-22.1 ± 43.2 (40) Median = -31.0	-20.8 ± 44.3 (38) Median = -28.1	-37.1 ± 30.6 (37) Median = -40.7
Urinary Pyridinium Crosslaps (Corrected for Creatinine)	38.5 ± 75.3 (38) Median = 27.3	-18.6 ± 54.7 (40) Median = -37.5	-11.4 ± 56.2 (38) Median = -24.6	-36.5 ± 38.6 (37) Median = -53.6
Urinary Hydroxyproline/Creatinine	11.4 ± 48.3 (38) Median = 3.7	-1.0 ± 102.4 (40) Median = -26.9	-13.5 ± 57.3 (38) Median = -28.1	-19.1 ± 48.0 (38) Median = -31.9
Urinary Calcium	62.4 ± 164.4 (38) Median = 2.9	-10.4 ± 58.8 (38) Median = -23.9	-8.6 ± 68.3 (38) Median = -13.1	-0.7 ± 65.3 (37) Median = -10.0

As depicted in Figures 2-6 (different sample sizes over time), all the 3 E₂ groups showed a reduction in the biochemical bone markers of interest by Month 6, while the placebo group

showed an increase. Then they were either further reduced or sustained throughout the rest of the 24-month treatment period.

Figure 2

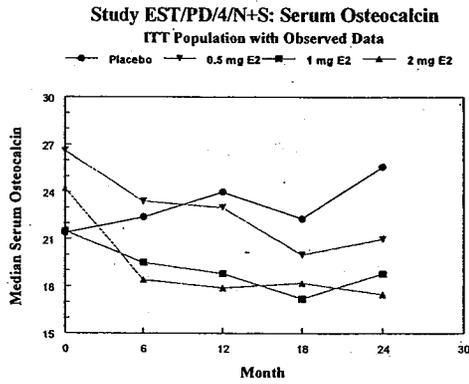


Figure 3

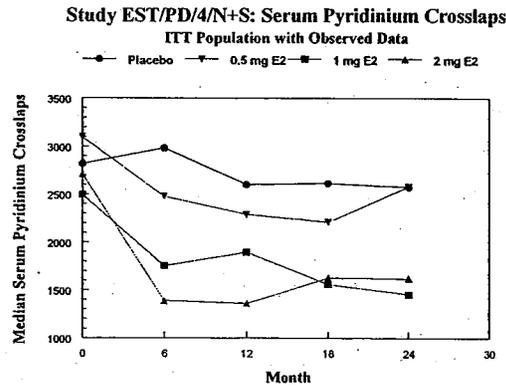


Figure 4

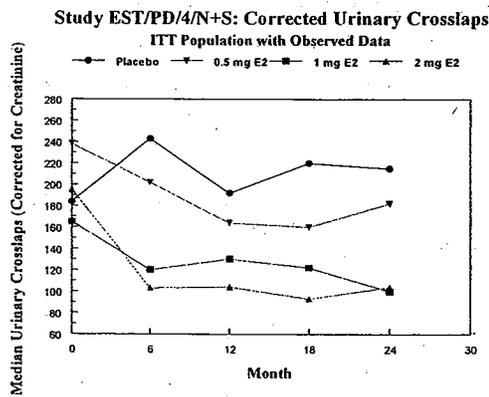


Figure 5

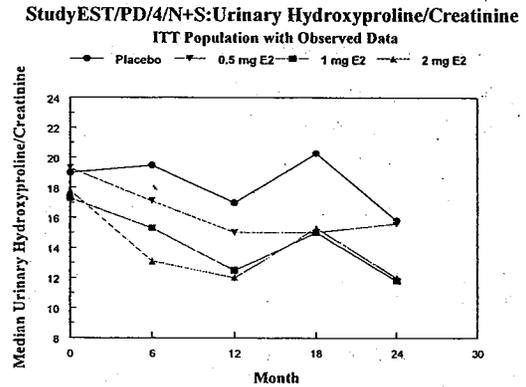
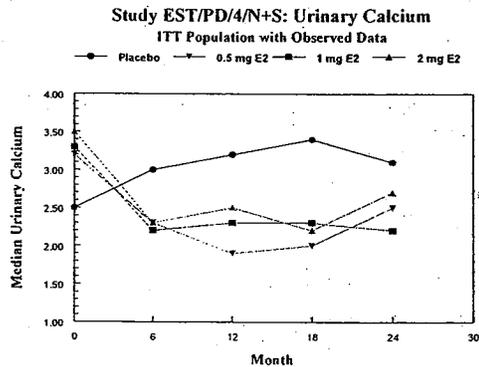


Figure 6



3.2 Evaluation of Safety

Safety is not the focus of this review. See Dr. Bill Lubas's review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Since all the study subjects were females and aged between 44 and 55 years, no subgroup analyses for gender and age were performed. Since no ethnic information was recorded in this study, no subgroup analysis for race was performed either.

4.2 Other Special/Subgroup Populations

Since the target population was postmenopausal women (defined by baseline FSH > 40 U/L), the reviewing medical officer requested treatment response of this sub-population alone for the % change from baseline in lumbar spine BMD at Month 24 to be evaluated as well. This reviewer employed the same analysis techniques as used in Section 3.1.5 and found that the efficacy outcomes (Table 10) were similar to the ones based on the whole study population (see Table 5). In fact, the treatment differences between the 3 E₂ doses and placebo were more numerically pronounced in postmenopausal women than in the whole study population.

Table 10 – Results for Lumbar Spine BMD – Postmenopausal Women Population Only

ITT (LOCF)	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
Raw mean lumbar spine BMD ± standard deviation (sample size)				
Month 0	1.15 ± 0.16 (22)	1.08 ± 0.11 (31)	1.15 ± 0.16 (22)	1.14 ± 0.14 (26)
Month 24	1.09 ± 0.17 (22)	1.07 ± 0.11 (31)	1.16 ± 0.16 (22)	1.17 ± 0.15 (26)
Raw mean % change from baseline ± standard deviation (sample size)				
Month 24	-4.63 ± 4.42 (22) Median = -4.54 95% CI (-6.6, -2.7)	-0.04 ± 3.25 (31) Median = -0.93 95% CI (-1.2, 1.2)	1.09 ± 3.59 (22) Median = 0.89 95% CI (-0.5, 2.7)	2.46 ± 3.31 (26) Median = 2.19 95% CI (1.1, 3.8)
Least-squares mean % change from baseline ± standard error (sample size)				
Month 24	-4.63 ± 0.78 (22)	-0.03 ± 0.67 (31)	1.09 ± 0.78 (22)	2.46 ± 0.72 (26)
Comparison against Placebo				
Treatment Difference		4.60	5.72	7.09
Dunnett's p-value		<0.0001	<0.0001	<0.0001
Dunnett's 95% CI		(2.15, 7.06)	(3.11, 8.33)	(4.58, 9.60)

To assess whether the treatment effects in the subgroups defined by menopausal status were statistically different, this reviewer performed a test for interaction between study groups and baseline FSH level (≤ 40 U/L [non-postmenopausal] vs. > 40 U/L [postmenopausal]). As shown in Table 11, treatment with any of the E₂ doses improved lumbar spine BMD relative

to placebo in each subgroup. However, there was a significant treatment-by-FSH level interaction ($p = 0.0254$), which was considered quantitative in nature rather than qualitative since treatment effects in the 2 subgroups were in the same direction.

Table 11 – Subgroup Analyses for Lumbar Spine BMD

ITT (LOCF)	Raw Mean % Change from Baseline at Month 24 ± SD (N)			
	Placebo	0.5 mg E ₂	1.0 mg E ₂	2.0 mg E ₂
FSH ≤ 40 U/L	-1.65 ± 3.23 (14)	-0.88 ± 3.63 (6)	0.46 ± 2.58 (14)	0.26 ± 2.43 (11)
FSH > 40 U/L	-4.63 ± 4.42 (22)	-0.04 ± 3.25 (31)	1.09 ± 3.59 (22)	2.46 ± 3.31 (26)

There were consistent treatment effects on % change from baseline in lumbar spine BMD at Month 24 across the subgroups defined by baseline lumbar spine BMD (≤ 1.0 , between 1.0 and up to 1.2, > 1.2 as suggested by the reviewing medical officer), center (Norway vs. Sweden), and oophorectomy performed (yes vs. no), as no significant treatment-by-subgroup interactions were observed ($p > 0.10$ in all cases).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In general, there were no serious statistical issues noted by this reviewer for the EST/PD/4/N+S study. As shown in Table 12 and Figure 7, the 0.5 mg, 1 mg, and 2 mg E₂ doses were all effective in improving BMD of lumbar spine, femoral neck, trochanter, and Wards triangle after 24 months of treatment when compared with the placebo. The significance was particularly evident in the case of lumbar spine BMD (the primary efficacy variable, see Table 5). However, when compared with baseline, a 0.17% mean (1% in terms of median) reduction in lumbar spine BMD at Month 24 was observed for the 0.5 mg E₂ group. The analyses based on the postmenopausal women population revealed similar findings to the ones based on the whole ITT population.

Table 12 – Study EST/PD/4/N+S: Summary Results for BMD – ITT Population with LOCF

ITT (LOCF)	Raw Mean % Change from Baseline at Month 24 ± SD (N)			
	Lumbar Spine	Femoral Neck	Trochanter	Wards Triangle
Placebo	-3.47 ± 4.22 (36)	-1.96 ± 3.94 (37)	-0.34 ± 5.54 (37)	-2.17 ± 6.46 (37)
0.5 mg E ₂	-0.17 ± 3.28 (37) *	1.76 ± 4.23 (36) *	0.97 ± 5.71 (36)	0.74 ± 6.01 (36)
1.0 mg E ₂	0.84 ± 3.21 (36) *	1.95 ± 4.33 (36) *	3.00 ± 4.88 (36) *	0.71 ± 6.41 (36)
2.0 mg E ₂	1.81 ± 3.21 (37) *	1.87 ± 5.19 (37) *	2.92 ± 4.81 (37) *	1.80 ± 6.84 (37) *

* = Significant at $p \leq 0.05$ when compared with placebo based on Dunnett's t-test

Figure 7

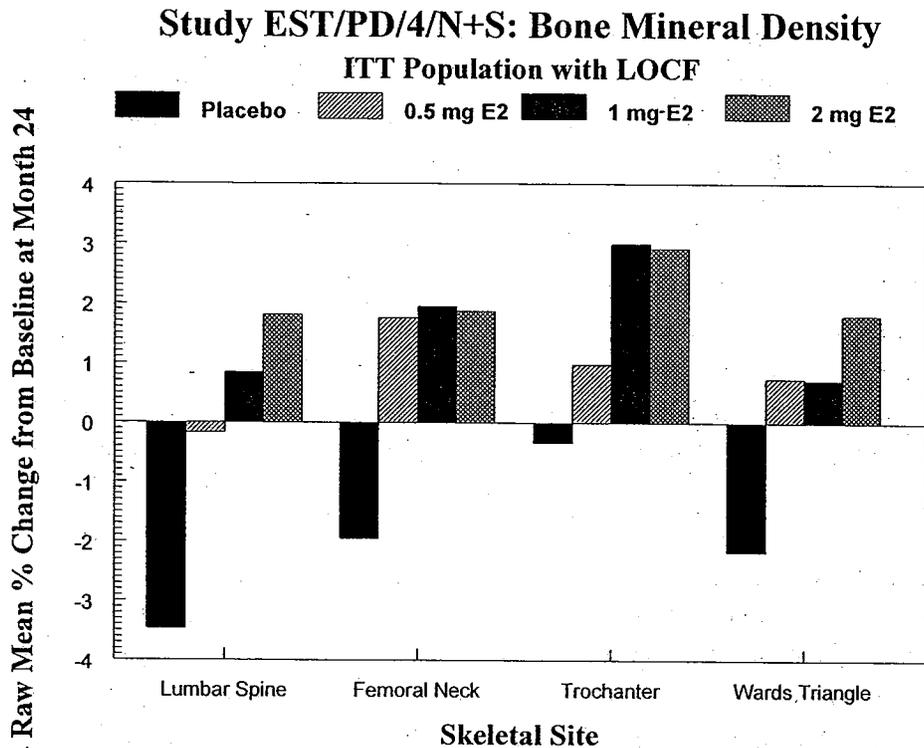


Table 13 summarizes the efficacy results for BMD of lumbar spine, femoral neck, and trochanter for the KLIM/PD/11/USA study (copied from the sponsor’s Tables 8.2.1.1. and 8.2.1.2. on pages 55, 57, and 58). According to the sponsor’s analysis results, all the treated groups showed a significantly increased mean % change from baseline in lumbar spine, femoral neck, and trochanter BMD at the end of the 24-month trial.

Table 13 – Study KLIM/PD/11/USA: Summary Results for BMD – ITT Population with LOCF

ITT (LOCF)	Raw Mean % Change from Baseline at Month 24 ± SD (N)		
	Lumbar Spine	Femoral Neck	Trochanter
Placebo	-2.12 ± 2.86 (37)	-2.26 ± 3.42 (37)	-1.95 ± 4.33 (37)
0.25 mg E ₂	0.39 ± 2.93 (37) *	0.28 ± 3.65 (37) *	0.84 ± 5.19 (37) *
0.5 mg E ₂	2.26 ± 2.76 (31) *	0.26 ± 2.86 (30) *	1.74 ± 4.12 (30) *
1.0 mg E ₂	2.76 ± 2.88 (37) *	1.63 ± 4.18 (36) *	2.53 ± 4.81 (36) *
1.0 mg E ₂ + 0.25 mg NETA	3.54 ± 3.68 (37) *	2.09 ± 3.08 (37) *	3.88 ± 3.71 (37) *
1.0 mg E ₂ + 0.5 mg NETA	3.80 ± 3.03 (37) *	1.76 ± 4.10 (37) *	3.66 ± 4.32 (37) *
2.0 mg E ₂ + 1.0 mg NETA	4.99 ± 3.75 (42) *	2.63 ± 4.29 (42) *	4.62 ± 5.27 (42) *

* = Significant at p ≤ 0.05 when compared with placebo, using an ANOVA model followed by Dunnett’s t-test

5.2 Conclusions and Recommendations

In the EST/PD/4/N+S study, the data have demonstrated that the 1 mg and 2 mg E₂ doses were effective in increasing BMD of lumbar spine and hip (femoral neck, trochanter, and Wards triangle) at the end of the 24-month treatment trial. The 0.5 mg E₂ dose, however, resulted in mean and median decreases in lumbar spine BMD from baseline at Month 24. Nevertheless, all 3 doses were better than placebo in preventing bone loss for postmenopausal women with a hysterectomy.

In the KLIM/PD/11/USA study, the data have demonstrated the effectiveness of the 0.5 mg E₂ dose in improving BMD of lumbar spine, femoral neck, and trochanter. In fact, all the treated doses (0.25 mg E₂, 0.5 mg E₂, 1 mg E₂, 1 mg E₂/0.25 mg NETA, 1 mg E₂/0.5 mg NETA, and 2 mg E₂/1 mg NETA) were significantly better than placebo in preventing bone loss for postmenopausal women with an intact uterus. Wards triangle was not evaluated in this trial.

5.3 Labeling Comments

The target population in the proposed labeling is postmenopausal women with an intact uterus. The EST/PD/4/N+S study was conducted in a population including some non-postmenopausal women. Also, all the study subjects had a hysterectomy. In addition, no calcium and/or Vitamin D were supplemented in this European study.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader

CC: HFD-510/PMadara, TKehoe, WLubas
HFD-715/TPermutt, TSahlroot, CLiu
HFD-700/ENevius, LPatrician

6. APPENDIX I

Sponsor's Test Results for BMD Spine (dependent variable is ln(last visit/baseline))

	N	p-value for treatment	
With covariates	138	0.0000	
With covariates postmenopausal women (p.w.) only	94	0.0000	
Without covariates	146	0.0000	
Per protocol (with covariates)	120	0.0000	

Contrasts:

	0.5 mg E2 - placebo	Estimate (95% C.I. for diff.)	
	p-value		
With covariates	0.0000	0.0364	(0.0199 - 0.0529)
With covariates p.w. only	0.0000	0.0493	(0.0299 - 0.0687)
Without covariates	0.0001	0.0340	(0.0176 - 0.0504)
Per protocol (with covariates)	0.0001	0.0390	(0.0197 - 0.0583)

	1.0 mg E2 - placebo	Estimate (95% C.I. for diff.)	
	p-value		
With covariates	0.0000	0.0472	(0.0309 - 0.0634)
With covariates p.w. only	0.0000	0.0607	(0.0401 - 0.0813)
Without covariates	0.0000	0.0442	(0.0277 - 0.0607)
Per protocol (with covariates)	0.0000	0.0507	(0.0326 - 0.0687)

	2.0 mg E2 - placebo	Estimate (95% C.I. for diff.)	
	p-value		
With covariates	0.0000	0.0542	(0.0380 - 0.0705)
With covariates p.w. only	0.0000	0.0732	(0.0530 - 0.0933)
Without covariates	0.0000	0.0537	(0.0373 - 0.0701)
Per protocol (with covariates)	0.0000	0.0571	(0.0390 - 0.0753)

Sponsor's Test Results for BMD Femoral Neck (dependent variable is ln(last visit/baseline))

	N	p-value for treatment	
With covariates	138	0.0002	
With covariates postmenopausal women (p.w.) only	94	0.0004	
Without covariates	146	0.0002	
Per protocol (with covariates)	122	0.0032	

Contrasts:

	0.5 mg E2 - placebo	Estimate (95% C.I. for diff.)	
	p-value		
With covariates	0.0002	0.0394	(0.0189 - 0.0600)
With covariates p.w. only	0.0004	0.0438	(0.0199 - 0.0677)
Without covariates	0.0004	0.0372	(0.0169 - 0.0575)
Per protocol (with covariates)	0.0081	0.0301	(0.0080 - 0.0521)

	1.0 mg E2 - placebo	Estimate (95% C.I. for diff.)	
	p-value		
With covariates	0.0003	0.0382	(0.0181 - 0.0582)
With covariates p.w. only	0.0024	0.0389	(0.0142 - 0.0636)
Without covariates	0.0002	0.0390	(0.0187 - 0.0593)
Per protocol (with covariates)	0.0005	0.0379	(0.0170 - 0.0589)

	2.0 mg E2 - placebo	Estimate (95% C.I. for diff.)	
	p-value		
With covariates	0.0007	0.0360	(0.0154 - 0.0565)
With covariates p.w. only	0.0001	0.0497	(0.0252 - 0.0743)
Without covariates	0.0003	0.0379	(0.0177 - 0.0580)
Per protocol (with covariates)	0.0044	0.0312	(0.0099 - 0.0525)

Sponsor's Test Results for BMD Trochanter (dependent variable is ln(last visit/baseline))

	N	p-value for treatment
With covariates	138	0.0064
With covariates postmenopausal women (p.w.) only	94	0.0319
Without covariates	146	0.0152
Per protocol (with covariates)	122	0.0297

Contrasts:

	0.5 mg E2 - placebo p-value	Estimate (95% C.I. for diff.)
With covariates	0.2027	0.0157 (-0.0085 - 0.0399)
With covariates p.w. only	0.2931	0.0164 (-0.0145 - 0.0473)
Without covariates	0.2853	0.0130 (-0.0109 - 0.0369)
Per protocol (with covariates)	0.5785	0.0074 (-0.0188 - 0.0335)

	1.0 mg E2 - placebo p-value	Estimate (95% C.I. for diff.)
With covariates	0.0044	0.0345 (0.0110 - 0.0581)
With covariates p.w. only	0.0254	0.0367 (0.0046 - 0.0688)
Without covariates	0.0066	0.0333 (0.0094 - 0.0573)
Per protocol (with covariates)	0.0156	0.0307 (0.0059 - 0.0555)

	2.0 mg E2 - placebo p-value	Estimate (95% C.I. for diff.)
With covariates	0.0022	0.0380 (0.0140 - 0.0621)
With covariates p.w. only	0.0076	0.0437 (0.0119 - 0.0754)
Without covariates	0.0075	0.0326 (0.0088 - 0.0564)
Per protocol (with covariates)	0.0186	0.0301 (0.0051 - 0.0551)

Sponsor's Test Results for BMD Wards Triangle (dependent variable is ln(last visit/baseline))

	N	p-value for treatment
With covariates	138	0.0235
With covariates postmenopausal women (p.w.) only	94	0.0215
Without covariates	146	0.0480
Per protocol (with covariates)	122	0.2967

Contrasts:

	0.5 mg E2 - placebo p-value	Estimate (95% C.I. for diff.)
With covariates	0.0457	0.0307 (0.0006 - 0.0607)
With covariates p.w. only	0.1074	0.0314 (-0.0069 - 0.0697)
Without covariates	0.0470	0.0298 (0.0004 - 0.0593)
Per protocol (with covariates)	0.3544	0.0157 (-0.0178 - 0.0492)

	1.0 mg E2 - placebo p-value	Estimate (95% C.I. for diff.)
With covariates	0.0279	0.0328 (0.0036 - 0.0620)
With covariates p.w. only	0.0421	0.0411 (0.0015 - 0.0808)
Without covariates	0.0505	0.0294 (-0.0001 - 0.0588)
Per protocol (with covariates)	0.1867	0.0212 (-0.0104 - 0.0527)

	2.0 mg E2 - placebo p-value	Estimate (95% C.I. for diff.)
With covariates	0.0034	0.0452 (0.0152 - 0.0751)
With covariates p.w. only	0.0023	0.0620 (0.0227 - 0.1013)
Without covariates	0.0079	0.0398 (0.0106 - 0.0690)
Per protocol (with covariates)	0.0614	0.0306 (-0.0015 - 0.0627)

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Cynthia Liu
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