

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-001

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO

NDA#: 22-001

Sponsor: Novo Nordisk, Inc

Drug: Activella (0.5mg E2/0.1 mg NETA)

Indication: Prevention of postmenopausal osteoporosis

Date of Submission: March 1, 2006

Primary Medical Reviewer: Bill Lubas, M.D., Ph.D.

I. Introduction and Background

Novo Nordisk, Inc. has submitted this new drug application for a lower dose Activella (0.5mg estradiol [E2]/0.1 mg norethindrone acetate [NETA]) tablet daily seeking approval for the prevention of osteoporosis in postmenopausal women with an intact uterus. The basis for approval is one randomized, 2-year study KLIM/PD/11/USA. This study did not utilize the to-be-marketed formulation of 0.5mg E2 / 0.1mg NETA and instead evaluated the estrogen only component, 0.5mg E2. The scientific basis for allowing a trial evaluating BMD changes of an estrogen-only drug to support the approval of a combination estrogen/progestin drug product is that there is clear evidence in the literature that the addition of a progestin is not in any way detrimental and may be additive to the positive BMD effects achieved with estrogen alone. Therefore, evidence suggests that the addition of 0.1mg NETA to 0.5mg E2, would be expected to increase LS BMD more effectively than 0.5mg E2 alone. Thus, if adequate BMD increases are shown with 0.5mg E2, it is presumed that this combination product of E2 and NETA will also show beneficial effects on bone density.

Activella (1.0mg E2/0.5mg NETA) is currently approved for the following in women who have a uterus:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.
- Treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Prevention of postmenopausal osteoporosis.

Current therapies available for the prevention of osteoporosis in postmenopausal women include oral estrogen preparations (Estrace, Femhrt, Ogen, Ortho-Est, Ortho-Prefest, Ortho-Tricyclen, Prefest, Premarin, Prempro, Premphase); transdermal estrogen preparations (Alora, Climara, ClimaraPro, Menostar, Vivelle); oral bisphosphonates (Fosamax, Actonel, Boniva); and calcitonin nasal spray (Miacalcin, Fortical).

II. Clinical Efficacy

The sponsor has submitted two studies to support approval of low dose Activella product. Study KLIM/PD/11/USA provides the data supporting approval of low dose Activella for prevention of osteoporosis in postmenopausal women with an intact uterus. This study was also the pivotal study relied upon for the approval of a higher dose of Activella (1 mg E2/0.5 mg NETA) for prevention of postmenopausal osteoporosis in women with an intact uterus in April, 2000. This study is discussed in detail. Study EST/PD/4/N+S provides supportive evidence for the efficacy of 0.5 mg E2 for increasing BMD and is also discussed.

II.a Study KLIM/PD/11/USA: This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group, 26-month study in healthy postmenopausal women with an intact uterus. The primary endpoint of the study was lumbar spine bone mineral density (BMD).

Study population: Subjects enrolled in the study were age greater than 45 years, 1 – 5 years post menopause with a bone mineral density T-score of ≤ -2.0 at the lumbar spine. The postmenopausal state was defined as serum E2 levels ≤ 20 pg/mL and FSH ≥ 40 mIU/mL. Women with a history of metabolic bone disease, osteoporotic fracture, myocardial infarction, obesity, abnormal bleeding or thrombophlebitis or significant hepatic or gallbladder disease were excluded from the study.

Study treatments: Eligible subjects were randomized to one of seven treatment groups: 2mg E2 + 1mg NETA; 1mg E2 + 0.5mg NETA; 1mg E2 + 0.25mg NETA; 1mg E2 only; 0.5mg E2 only; 0.25mg E2 only; or placebo. All subjects also received daily calcium (1000mg calcium). No vitamin D (400 - 500IU D) supplementation was provided.

Efficacy measures: The primary efficacy endpoint was percent change in lumbar spine BMD. Secondary efficacy endpoints included femoral neck and trochanter BMD. Bone density measurements, determined by dual x-ray absorptiometry (DXA), were obtained at baseline, 13, 19, and 26 months. Laboratory measurements of bone turnover markers included the bone formation marker, serum bone-specific alkaline phosphatase and bone resorption markers serum urinary pyridinoline and urinary deoxypyridinoline were obtained at baseline and Months 6, 13, 19, and 26.

Results:

Disposition: A total of 737 subjects were screened and 327 subjects were enrolled into the study and 189 (58%) subjects completed the study. As outlined in the table below, of the 138 (42%) subjects who withdrew from the study, 65 (20%) withdrew due to adverse events, 44 (13%) withdrew due to noncompliance and 29 (9%) withdrew for other reasons. There was comparable subject disposition between the placebo group and the 0.5mg E2 group.

Study KLIM/PD/11/USA: Patient Disposition							
	plac	0.25 E2	0.5 E2	1.0 E2	1.0 E2 + 0.25 NETA	1.0 E2 + 0.5 NETA	2.0 E2 + 1.0 NETA
N, treated	48	45	44	46	49	47	48
Discontinued	19 (40)	20 (44)	20 (46)	26 (56)	18 (37)	19 (40)	16 (33)
AE	11 (23)	9 (20)	6 (14)	16 (35)	7 (14)	8 (17)	8 (17)
Noncompliance	6 (12)	7 (16)	8 (18)	6 (13)	6 (12)	5 (11)	6 (12)
Other	2 (4)	4 (9)	6 (14)	4 (9)	5 (10)	6 (13)	2 (4)
Completed	29 (60)	25 (56)	24 (54)	20 (44)	31 (63)	28 (60)	32 (67)

Demographics: As outlined in the table below, baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was approximately 53 years. The mean time since last menses ranged from 2.5 – 3.1 years. Overall 103 subjects, 31% of the enrolled population had low bone mass at baseline with a BMD T-score of less than -2.0. Subjects with BMD in the osteoporotic range or with a prevalent osteoporotic fracture were excluded from the study.

Study KLIM/PD/11/USA: Patient Demographics							
	plac	0.25 E2	0.5 E2	1.0 E2	1.0 E2 + 0.25 NETA	1.0 E2 + 0.5 NETA	2.0 E2 + 1.0 NETA
N, treated	48	45	44	46	49	47	48
Age (yrs, mean)	53.5	53.2	52.3	52.7	52.4	52.5	53.1
Weight (kg, mean)	67.2	70.9	68.0	69.7	67.8	67.8	66.9
Height (cm, mean)	163	161	162	165	162	163	163
BMI (mean)	25.2	27.1	25.8	25.5	25.6	25.3	25.1
Last menses (yrs)	3.1	3.1	2.5	2.6	2.8	3.1	2.8
LS BMD (gm/cm ²)	1.09	1.10	1.07	1.09	1.09	1.11	1.05
Osteopenia (%)	31	20	39	35	27	30	40

Lumbar spine BMD: Change in lumbar spine BMD was the primary efficacy endpoint of the study. As outlined in the table below, with the exception of placebo, increases in lumbar spine BMD were seen in all treatment groups. The 0.5 mg E2 group had an increase in LS BMD of 2.8% with a treatment difference of 4.4% compared to placebo ($p < 0.001$). Seventy four percent of subjects in this group exhibited no change or a gain in BMD over the treatment period.

The findings noted with the 1.0 mg E2 groups support the premise that the addition of NETA is not detrimental and appears to be additive to the positive BMD effects achieved with estrogen alone. The 1.0mg E2 only group achieved an increase of 2.8% in lumbar spine BMD, compared to the 3.5% increase seen in the 1.0mg E2 /0.25mg NETA group and 3.8% increase seen in the 1.0mg E2 /0.5mg NETA group.

Study KLIM/PD/11/USA: Percent Change in LS BMD at Month 26, LOCF							
	plac	0.25 E2	0.5 E2	1.0 E2	1.0 E2 + 0.25 NETA	1.0 E2 + 0.5 NETA	2.0 E2 + 1.0 NETA
N, LOCF	37	37	31	37	37	37	42
Mean % Change	-2.12	0.39	2.26	2.76	3.54	3.80	4.99

Study KLIM/PD/11/USA: Percent Change in LS BMD at Month 26, LOCF							
	plac	0.25 E2	0.5 E2	1.0 E2	1.0 E2 + 0.25 NETA	1.0 E2 + 0.5 NETA	2.0 E2 + 1.0 NETA
SD	2.86	2.93	2.76	2.88	3.68	3.03	3.75
Compared to Placebo							
Difference		2.51	4.37	4.88	5.66	5.92	7.11
p-value		0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Responders [n (%)]	8 (22)	21 (57)	23 (74)	32 (86)	30 (81)	32 (86)	38 (90)
responder = \geq 0% change in BMD, baseline - LOCF							

Femoral Neck and Trochanter BMD: As outlined in the table below, treatment with study drug resulted in smaller but significant increases in BMD at the femoral neck and trochanter. At the femoral neck, the 0.5 mg E2 group had an increase in BMD of 0.3% compared to placebo (-2.3%, $p=0.007$). Fifty-seven percent of subjects in this group exhibited no change or a gain in femoral neck BMD over the treatment period. At the trochanter, the 0.5 mg E2 group had an increase in BMD of 1.7% compared to placebo group's -2.0%. Sixty-eight percent of subjects in this group exhibited no change or a gain in trochanter BMD over the treatment period.

Study KLIM/PD/11/USA: Percent Change in Hip BMD at Month 26, LOCF							
	plac	0.25 E2	0.5 E2	1.0 E2	1.0 E2 + 0.25 NETA	1.0 E2 + 0.5 NETA	2.0 E2 + 1.0 NETA
Femoral Neck							
N, LOCF	37	37	30	36	37	37	42
Mean % Change	-2.26	0.28	0.26	1.63	2.09	1.76	2.63
SD	3.42	3.65	2.86	4.18	3.08	4.10	4.29
Compared to Placebo							
Difference		2.54	2.52	3.89	4.35	4.02	4.89
p-value		0.004	0.007	<0.001	<0.001	<0.001	<0.001
Responders [n (%)]	10 (27)	22 (60)	17 (57)	23 (64)	28 (76)	23 (62)	32 (76)
Trochanter							
N, LOCF	37	37	31	37	37	37	42
Mean % Change	-1.95	0.84	1.74	2.53	3.88	3.66	4.62
SD	4.32	5.19	4.12	4.81	3.71	4.32	5.27
Compared to Placebo							
Difference		2.79	4.48	4.48	5.83	5.61	6.57
p-value		0.014	0.002	<0.001	<0.001	<0.001	<0.001
Responders [n (%)]	12 (32)	21 (57)	20 (68)	26 (72)	33 (89)	32 (86)	35 (83)
responder = \geq 0% change in BMD, baseline - LOCF							

Biochemical Markers of Bone Turnover: Markers of bone turnover included serum bone-specific alkaline phosphatase, urinary pyridinoline and urinary deoxypyridinoline. In general, the biochemical marker response to study drug supports the BMD response seen. The change in bone resorption was evaluated by the pyridinolines. In the placebo group, the median change in urinary pyridinoline was -6% (range -64% to +87%), compared to the 0.5mg E2 group where the median change was -22% (range -49% to +118%). For deoxypyridinoline, the placebo group exhibited a median change of -9% (range -67% to

+155%), compared to the 0.5mg E2 group where the median change was again -22% (range -66% to +58%). For bone-specific alkaline phosphatase, a marker of bone formation, the placebo group had a median change of +114% (range -39% to +1476%) compared to the 0.5mg E2 group where the median change was again +90% (range -51% to +2062%). When compared to newer markers such as N-telopeptide and C-telopeptide, the pyridinolines tend to be nonspecific as markers of bone resorption, as seen with the wide range of responses exhibited.

Conclusions: Estradiol 0.5mg daily had statistically significant increases in lumbar spine, femoral neck and trochanter BMD, when compared to placebo. The biochemical markers of bone turnover, urinary pyridinoline and deoxypyridinoline decreased in the estrogen-treated group and compared to placebo, evidencing the anti-resorptive effects of estrogen. Findings in this study support the conclusion that the addition of a progestin may have an additive benefit for BMD compared to estrogen alone and allow for bridging of the data from the 0.5mg E2 group to support the efficacy of the 0.5mg E2 / 0.1mg NETA combination product. Fracture risk reduction efficacy was not directly assessed and is presumed. Therefore, product labeling should only outline the BMD effects demonstrated.

II.b Study EST-PD-4-N+S: This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group, 24-month study conducted in Norway and Sweden. The primary endpoint of the study was lumbar spine bone mineral density (BMD).

Study population: Subjects enrolled in the study were age 45 to 55 years, peri-menopause or post menopause, status post hysterectomy (\pm oophorectomy) with a serum FSH \geq 20 mIU/mL. There were no bone mineral density (BMD) criteria for enrollment, although women with known metabolic bone disease or osteoporosis were excluded. Women with a history of prior estrogen or other steroid use, breast carcinoma, deep venous thrombosis, thromboembolic disorders, cerebrovascular or cardiovascular disease or significant hepatic or gallbladder disease were excluded from the study.

Study treatments: Eligible subjects were randomized to one of four treatment groups: 2mg E2, 1mg E2, 0.5mg E2, or placebo. No calcium or vitamin D (400 - 500IU D) supplementation was provided. The lack of calcium supplementation

Efficacy measures: The primary efficacy endpoints included percent change in lumbar spine BMD, percent change in femoral neck and trochanter BMD. Bone density measurements, determined by dual x-ray absorptiometry (DXA), were obtained at baseline, 6, 12, 18, and 24 months. Laboratory measurements of bone turnover markers included the bone formation marker, serum osteocalcin and bone resorption markers serum pyridinoline, urinary pyridinoline and urinary hydroxyproline were also obtained at baseline, 6, 12, 18, and 24 months.

Results:

Disposition: A total of 171 subjects were enrolled, 166 subjects received study medication and 139 (84%) subjects completed the study. As outlined in the table below, of the 27 (16%) subjects who withdrew from the study, 20 (12%) withdrew due to adverse events, 5 (3%) withdrew due to noncompliance and 2 (1%) withdrew for other reasons. Fewer subjects withdrew from the 0.5mg E2 group compared to the placebo group.

Study EST-PD-4-N+S: Patient Disposition				
	plac	0.5 E2	1.0 E2	2.0 E2
N, treated	43	40	41	42
Discontinued	12 (28)	3 (8)	6 (15)	6 (14)
AE	10 (23)	1 (2)	5 (12)	4 (10)
Noncompliance	1 (2)	2 (5)	0 (0)	2 (5)
Other	1 (2)	0 (0)	1 (2)	0 (0)
Completed	31 (72)	37 (92)	35 (85)	36 (86)

Demographics: As outlined in the table below, baseline subject demographics were generally well balanced across the treatment groups. The average age of enrollees was approximately 50 years. The mean time since hysterectomy ranged from 3.4 – 4.5 years. Overall, 58 (35%) subjects also had bilateral oophorectomy performed with their hysterectomy. Median lumbar spine BMD was well within the normal range at baseline. Low bone mass was not an enrollment criteria. Subjects with a diagnosis of osteoporosis or a prevalent osteoporotic fracture were excluded from the study.

Study EST-PD-4-N+S: Patient Demographics				
	plac	0.5 E2	1.0 E2	2.0 E2
N, treated	43	40	41	42
Age (yrs, mean)	49.6	49.9	49.1	49.5
Weight (kg, mean)	70.8	69.6	67.8	69.5
Height (cm, mean)	167	168	166	168
BMI (mean)	25.6	24.5	24.7	24.7
Time since hysterectomy (yrs)	4.4	4.4	3.4	4.5
Oophorectomy (n, %)	11 (26)	14 (35)	16 (39)	17 (40)
LS BMD (gm/cm ²)	1.198	1.100	1.157	1.160

Lumbar spine BMD: Change in lumbar spine BMD was the primary efficacy endpoint of the study. As outlined in the table below, both the placebo and 0.5 mg E2 groups had decreases in lumbar spine BMD. The placebo group had a mean BMD loss of 3.5% while the 0.5 mg E2 group had a mean loss of 0.2%. The treatment difference was statistically significant at +3.3% (p < 0.0001). Forty-one percent of subjects in the 0.5mg E2 group exhibited no change or a gain in BMD over the treatment period.

Study EST-PD-4-N+S: Percent Change in LS BMD at Month 26, LOCF				
	plac	0.5 E2	1.0 E2	2.0 E2
N, treated	36	37	36	37
Mean % Change	-3.47	-0.17	0.84	1.81
SD	4.22	3.28	3.21	3.21

Study EST-PD-4-N+S: Percent Change in LS BMD at Month 26, LOCF				
	plac	0.5 E2	1.0 E2	2.0 E2
Compared to Placebo				
Difference		3.3	4.3	5.3
p-value		<0.0001	<0.0001	<0.0001
Responders (%)	19	41	61	68
responder = $\geq 0\%$ change in BMD, baseline - LOCF				

Femoral Neck and Trochanter BMD: As outlined in the table below, the placebo group sustained a decrease in BMD at both hip sites measured, while the E2 group had increases in BMD. At the femoral neck, the 0.5 mg E2 group had an increase in BMD of 1.8% compared to placebo (2.0%, $p < 0.001$). Sixty-nine percent of subjects in this group were responders with no change or a gain in femoral neck BMD over the treatment period. At the trochanter, the 0.5 mg E2 group had an increase in BMD of 1.0% compared to placebo group's -0.3%. Fifty-six percent of subjects in this group exhibited no change or a gain in trochanter BMD over the treatment period.

Study EST-PD-4-N+S: Percent Change in Hip BMD at Month 24, LOCF				
	plac	0.5 E2	1.0 E2	2.0 E2
Femoral Neck				
N, LOCF	36	37	36	37
Mean % Change	-1.96	1.76	1.95	1.87
SD	3.94	4.23	4.33	5.19
Compared to Placebo				
Difference		3.8	4.0	3.9
p-value		<0.001	<0.001	<0.001
Responders [n (%)]	27	69	69	59
Trochanter				
N, LOCF	36	37	36	37
Mean % Change	-0.34	0.97	3.0	2.92
SD	5.54	5.71	4.88	4.81
Compared to Placebo				
Difference		1.3	3.3	3.2
p-value		NS	<0.01	<0.01
Responders [n (%)]	38	56	78	78
responder = $\geq 0\%$ change in BMD, baseline - LOCF				

Biochemical Markers of Bone Turnover: Markers of bone turnover included serum osteocalcin, serum pyridinium crosslinks, urinary pyridinium crosslinks and urinary hydroxyproline. In general, the biochemical marker response to study drug supports the BMD response seen. The change in bone resorption was evaluated by the pyridinium crosslinks and hydroxyproline. In the placebo group, the median change in serum pyridinium crosslinks was +16% compared to the 0.5mg E2 group where the median change was -22%. For urinary pyridinium crosslinks, the placebo group exhibited a median change of +27%, compared to the 0.5mg E2 group where the median change was -19%. For urinary hydroxyproline the placebo group exhibited a median change of +4%, compared to the 0.5mg E2 group where the median change was -27%. For serum

osteocalcin, a marker of bone formation, the placebo group had a median change of +6.8% compared to the 0.5mg E2 group where the median change was again -19%.

Conclusions: Estradiol 0.5mg daily resulted in a mean and median decrease in lumbar spine BMD. Despite the bone loss seen 0.5mg E2 was statistically better than placebo at preserving bone density. The biochemical markers of bone turnover, serum pyridinium crosslinks, urinary pyridinium crosslinks and urinary hydroxyproline decreased in the estrogen-treated group and compared to placebo, evidencing the anti-resorptive effects of estrogen. Fracture risk reduction efficacy was not directly assessed and is presumed. While this study provides support for the effectiveness of 0.5mg estradiol, there are several critical elements of the study that outline differences between the study population and the proposed treatment population. These include: a study population of women status post hysterectomy when there would be no reason to treat women who have undergone hysterectomy with a combination estrogen progestin product; and the inclusion of peri-menopausal women in the study population. Currently, there is no current indication or data showing benefit for the prevention of PMO in peri-menopausal women. In addition, the lack adequate calcium supplementation most likely led to the increased bone loss seen in the placebo group. This information could be misleading in the label, suggesting added benefit for E2/NETA when there is none. Therefore, data from this study should not appear in the Activella label.

III. Clinical Safety

Three studies are included in the safety review conducted by Dr. Lubas. Study KLIM/PD/11/USA is the multicenter, double-blind, randomized, placebo-controlled, 26-month study in healthy postmenopausal women with an intact uterus. Study EST-PD-4-N+S is the multicenter, double-blind, randomized, placebo-controlled, 24-month study in peri- and post-menopausal women status post hysterectomy. These two studies evaluated 0.5mg estradiol and did not include the low dose Activella combination product (0.5mg E2 / 0.1 mg NETA). Study ALD-1537 did evaluate the safety 0.5mg E2 / 0.1 mg NETA. This was a multicenter, double-blind, randomized, placebo-controlled, 6-month study in symptomatic postmenopausal women. Study ALD-1537 is the focus of this safety review as it provides the only safety data available for the to-be-marketed formulation.

Disposition and exposure: A total of the 67 (12%) subjects withdrew from the study and 508 (88%) subjects completed the study. The incidence of withdrawal was higher in the placebo group (20%) than both the 0.5 E2/ 0.1 NETA (9%) and 0.5 E2/ 0.25 NETA (6%) treatment groups. The major reason for the difference in withdrawal rate was the higher incidence of ineffective therapy in the placebo group (8%) compared with the 0.5 E2/ 0.1 NETA (2%) and 0.5 E2/ 0.25 NETA (1%) groups.

Study ALD-1537: Patient Disposition				
	placebo	0.5 E2 / 0.25 NETA	0.5 E2 / 0.1 NETA	All
N, treated	200	181	194	575

Study ALD-1537: Patient Disposition				
	placebo	0.5 E2 / 0.25 NETA	0.5 E2 / 0.1 NETA	All
Discontinued	40 (20)	10 (6)	17 (9)	67 (12)
AE	16 (8)	4 (2)	11 (6)	31 (5)
Ineffective therapy	16 (8)	2 (1)	3 (2)	21 (4)
Noncompliance	2 (1)	2 (1)	3 (2)	7 (1)
Other	6 (3)	2 (1)	0 (0)	8 (1)
Completed	160 (80)	171 (94)	35 (85)	508 (88)

The mean duration of exposure to study drug was 21.4 ± 6.9 weeks for the placebo group, 23.8 ± 4.1 weeks for the 0.5 E2/ 0.25 NETA group and 23.6 ± 4.7 weeks for the 0.5 E2/ 0.1 NETA group.

Deaths, serious adverse events, and adverse events leading to withdrawal: One death was reported during the trial, a 57 year-old woman who received placebo, experienced a fatal myocardial infarction.

A total of 14 additional subjects experienced SAEs: 5 (1%) in the 0.5 E2/ 0.25 NETA group, 6 (1%) in the ALD 0.5 E2/ 0.1 NETA group and 3 (1%) in the placebo group. One subject in the 0.5 E2/ 0.25 NETA group withdrew due to breast cancer which the Sponsor possibly attributed to study drug.

A total of 31 subjects withdrew from the study because of adverse events, 4 (2%) subjects in the 0.5 E2/ 0.25 NETA group and 11 (6%) subjects in the 0.5 E2/ 0.1 NETA group, and 16 (8%) subjects in the placebo group.

Adverse events: Overall, 139 (70%) placebo-treated subjects, 127 (70%) 0.5 E2/ 0.25 NETA-treated subjects and 147 (76%) of 0.5 E2/ 0.1 NETA-treated subjects reported at least one adverse event. The most common adverse events were headache [38 (19%) placebo group, 47 (26%) 0.5 E2/ 0.25 NETA group and 42 (22%) of 0.5 E2/ 0.1 NETA group] and vaginal hemorrhage [24 (12%) placebo group, 39 (22%) 0.5 E2/ 0.25 NETA group and 51 (26%) of 0.5 E2/ 0.1 NETA group].

Adverse events of special interest

Fracture: Two subjects sustained a fracture during this short trial, both in the 0.5 E2/ 0.1 NETA treatment group. A 54 year woman sustained an ankle fracture and a 60 year old woman sustained a finger fracture.

Cardiovascular Adverse Events: There was no evidence of an increase in cardiovascular events in this 6 month study. Cardiovascular events occurred in 2% of subjects treated with 0.5 E2/ 0.25 NETA, 4% of subjects treated with 0.5 E2/ 0.1 NETA, and 6% of subjects in the placebo group. As previously discussed, one subject treated with placebo died of a myocardial infarction. In addition, a 58 year old woman treated with placebo sustained a transient ischemic attack.

Breast Adverse Events: Breast cancer is a concern with prolonged estrogen use. One subject, a 64 year old woman in the 0.5 E2/ 0.25 NETA treatment group was diagnosed with breast cancer after being treated for 173 days during the course of the trial. She had received hormone replacement products for 13 years prior to being enrolled in this study. Therefore, it is considered unlikely that the study drug was solely responsible for this adverse event.

Clinical symptoms relating to the breast (breast discomfort, breast pain and tenderness) were reported by $\leq 2\%$ of subjects treated with active drug, which was comparable with the placebo group. Mammography was performed at baseline and Month 6 on a subset of 255 subjects not previously treated with estrogen. No overall treatment differences were detected between the treatment groups and placebo. Visual assessment according to the Wolfe classification and the percentage scale showed no increase in breast density after 24 weeks of treatment with the low dose E2/NETA preparations.

Uterine Adverse Events: Endometrial hyperplasia is a concern with prolonged unopposed estrogen use and with combination products containing an insufficient progestin component. The incidence of endometrial thickening $\geq 5\text{mm}$ was 6% (11 subjects) in the 0.5 E2/ 0.25 NETA group, 10% (19 subjects) in the 0.5 E2/ 0.1 NETA group and 6% (8 subjects) in the placebo group. The distribution of endometrial thickness changes between the three treatment groups was very similar and changes primarily ranged between -2 mm and +2 mm with some cases occurring outside (above and below) these values. All enrolled subjects had a normal PAP test at screening. At week 24, one subject in the 0.5 E2/ 0.1 NETA group and one subject in the placebo group had abnormal PAP test findings.

Laboratory evaluations: Laboratory adverse events were reported in seven subjects. In the placebo group, four laboratory adverse events were reported: hematuria, leukocyturia, increased cholesterol and increased triglycerides. In the 0.5 E2/ 0.10 NETA group, one subject was noted to have increased liver function tests and study drug was subsequently withdrawn. In the 0.5 E2/ 0.25 NETA group, one subject reported increased triglycerides and a second subjects was reported to have decreased folate levels. There were no clinically relevant changes noted for chemistry and hematology parameters at Weeks 12 and 24.

As outlined in Dr. Lubas' review, both active drug combinations showed neutral or favorable changes in lipid and lipoprotein levels, blood clotting parameters and glucose metabolism.

Vital Signs: There were no clinically significant changes in vital signs in this study. One 54 year-old subject receiving placebo, reported weight gain and study drug was discontinued.

Conclusions: In this 6-month trial, no new safety signals were noted. Adverse events known to occur with estrogen + progestin therapy were seen with both active treatment groups. While there was no evidence of an increase in breast cancer risk, breast disease or cardiovascular events when compared to placebo, it is not possible to definitively

broaden these data from a short term 6 month trial to longer durations of therapy. For that reason, the current labeling recommendations of "*When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered*" in use for higher dose E2/NETA should be continued for the lower dose preparation.

IV. Pharmacology/Toxicology

There are no new Pharmacology / Toxicology data submitted in this NDA.

V. Clinical Pharmacology

The new pharmacokinetic data from study ALD-1640 was formally reviewed by Dr. Sandra Suarez of the Division for Reproductive and Urologic Products. The prespecified confidence intervals for the relative bioavailability of estradiol, estrone and NETA were within the acceptable range of 0.80 to 1.25. No new pharmacodynamic data was submitted in this NDA.

VI. CMC

The Chemistry review was formally conducted by Dr. Yvonne Yang. She recommends Approval, pending an overall acceptable cGMP recommendation from Compliance. An overall acceptable cGMP status was granted by the Office of Compliance on 12/15/2006.

VII. Other Regulatory Requirements

VIIa. Financial Disclosure

Dr. Zawadzki previously reviewed the financial disclosure information for study KLIM/PD/11/USA as part of NDA 21-103 and found them to be acceptable. Study EST/PD/4/N+S was conducted in 1998 and no financial disclosure information was required or collected prior to the time line when financial disclosure was required. Dr Lubas reviewed the financial disclosure information for studies ALD-1640 and ALD-1537, and found them acceptable.

VIIb. Pediatrics

The proposed indication in this sNDA is restricted to women after the onset of menopause. The PREA pediatric study requirements for the indication proposed in this sNDA should be waived.

VIIc. Clinical Audits/Inspections

A DSI audit was not conducted for this submission.

VIII. Conclusions and Recommendations

VIII.a. Conclusions

No new safety signals were noted in the single 6-month study that utilized the proposed low dose combination estrogen/progestin product. Adverse events known to occur with estrogen + progestin therapy were seen with both active treatment groups.

Estradiol 0.5mg daily had statistically significant preservation of BMD or increases in BMD of the lumbar spine, when compared to placebo. The differences noted between the two efficacy trials are most likely due to the lack of calcium supplementation in study EST-PD-4-N+S. Calcium supplementation is known to exert positive effects on BMD. In the two efficacy trials, the responder rate for lumbar spine BMD (subjects with no change or an increase in BMD) was 74% in the study where calcium supplementation was given and 41% in the study without calcium supplementation. Additional concerns regarding study EST-PD-4-N+S include the study population. This study enrolled only women who had a hysterectomy and therefore, would not require a combination estrogen/progestin product. In addition, the study enrolled peri-menopausal women, for whom the benefit of estrogen replacement to preserve bone density is not clear. Therefore, I agree with Dr. Lubas that data from study EST-PD-4-N+S could be misleading and should not appear in the Activella label.

VIIIb. Recommendation

Approve, with the agreed-upon labeling changes

**This is a representation of an electronic record that was signed electronically and
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/s/

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CLINICAL REVIEW

Application Type NDA
Submission Number 22-001
Submission Code N000

Letter Date February 28, 2006
Stamp Date March 1, 2006
PDUFA Goal Date January 1, 2007

Reviewer Name William Lubas, M.D., Ph.D.
Review Completion Date December 14, 2006

Established Name (estradiol/norethindrone
acetate)
(Proposed) Trade Name Activella®
0.5mg E2/0.1mg NETA
Therapeutic Class Osteoporosis-HRT
Applicant Novo Nordisk Inc.

Priority Designation S

Formulation Oral tablet
Dosing Regimen Once daily
Indication Prevention of postmenopausal
osteoporosis
Intended Population postmenopausal women with an
intact uterus

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Activella 0.5mg estradiol (E2)/0.1 mg norethindrone acetate (NETA) should be approved for the prevention of postmenopausal osteoporosis.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is recommended as this is a lower strength of an already approved product.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Activella 1mg E2/0.5 mg NETA was approved in April 2000 for the prevention of postmenopausal osteoporosis. In June 2002 the Women's Health Initiative Study (WHI) reported higher rates of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women during 5 years of treatment with oral conjugated estrogens combined with progesterone relative to placebo. As a result of this all estrogen products marketed in the US now include a black box warning suggesting that they be given at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. In response to recent US and European regulatory authority guidances the sponsor has submitted a lower strength dosage form of Activella, 0.5mg E2/0.1 mg NETA, for this same indication.

The sponsor submitted two 2-year trials, EST/PD/4/N+S and KLIM/PD/11/USA, supporting the use of 0.5 mg E2 for the prevention of osteoporosis in postmenopausal women. Even though these studies did not contain the to-be-marketed formulation, Activella 0.5mg E2/0.1 mg NETA,

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data from these trials was intended to support the efficacy of this combination estradiol/progestin formulation. These studies were reviewed by DMEP. The sponsor also submitted a 6 month trial, ALD-1537, for the treatment of moderate to severe vasomotor symptoms in postmenopausal women, and a single-dose, cross-over PK study, ALD-1640, with the to-be-marketed formulation (e.g. Activella 0.5mg E2/0.1mg NETA) which were reviewed by DRUP. Both divisions collaborated on the final label negotiated with the sponsor.

1.3.2 Efficacy

Study EST/PD/4/N+S was inadequately designed to support the proposed postmenopausal osteoporosis indication, and was not used to support labeling of the new low dose product. Data from the KLIM/PD/11/USA trial showed that 0.5mg of E2 alone is statistically better than placebo at maintaining lumbar spine, proximal femur and femoral trochanter BMD. In addition, data from this same trial showed that at a constant E2 dose BMD values at the lumbar spine, proximal femur and femoral trochanter were greater after treatment with combination tablets containing 0.25 and 0.5mg NETA than when patients were treated with tablets without NETA. Therefore, the addition of 0.1mg NETA to 0.5mg E2, in the to-be-marketed formulation, would be expected to increase LS BMD more effectively than 0.5mg E2 alone, and support the use of this formulation in the treatment of PMO.

1.3.3 Safety

The incidence and types of treatment related adverse events seen in the trials reviewed in this submission were not unexpected for estrogen replacement therapy. Breast pain was seen more commonly with combined estrogen/progestin formulations whereas endometrial hyperplasia/postmenopausal bleeding were seen primarily in the estrogen alone groups. While these ½ to 2-year studies showed no evidence of an increase in cardiovascular events, worsening of potential markers for cardiovascular disease or an increase in the risk for breast cancer with low dose estrogen compared to placebo, it is not possible to compare these data to longer studies like the 5-year WHI. Therefore, with sufficient treatment exposure it is still possible that higher rates of myocardial infarction, stroke, pulmonary emboli, deep venous thrombosis or invasive breast cancer may be seen in postmenopausal women treated with low dose oral conjugated estrogens compared to placebo. For this reason, use of this low dose estrogen/progestin formulation should continue to be limited to the shortest duration necessary consistent with treatment goals. In addition, women with hypertension, active cardiovascular disease, thromboembolic disorders or suspicious lesions by mammogram were not included in these trials so the risk profile for such patients was not assessed, and use in these subpopulations cannot be recommended.

1.3.4 Dosing Regimen and Administration

The proposed regimen is one tablet of Activella 0.5mg E2/0.1mg NETA daily to be given for the shortest duration consistent with treatment goals and risks for the individual woman. This is a low dose estrogen version of Activella which was originally approved in April 2000 for the treatment of postmenopausal osteoporosis as Activella 1mg E2/0.5mg NETA.

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1.3.5 Drug-Drug Interactions

Study ALD-1640 reviewed by Sandra Suarez in DRUP, confirmed that coadministration of E2 (0.5 to 1mg) and NETA (0.1 to 0.5mg) did not affect the pharmacokinetics of either E2 or NETA, consistent with information which is already present in the currently approved Activella 1mg E2/0.5mg NETA label. No other drug-drug interaction studies were included in this submission.

1.3.6 Special Populations

A pediatric waiver was granted because it is inappropriate to give hormone replacement therapy to pediatric patients to treat osteoporosis.

No geriatric studies were done as the indication is for short term treatment of postmenopausal women.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Activella® contains 0.5 mg of estradiol (E2) and 0.1mg of norethindrone acetate (NETA). The estrogen component 17 β -estradiol is identical to endogenous human estradiol. Administration of 17 β -estradiol to postmenopausal women has been shown to reduce the vasomotor symptoms associated with estrogen deficiency such as hot flushes and night sweats, and can prevent bone loss. The progestin component norethindrone acetate is a potent synthetic 19-norethisterone derivative. Norethindrone acetate is used in combination with estrogens in women with intact uteruses to reduce the risk associated with the proliferative effect of estrogen on the endometrium.

Activella (1 mg E2/0.5 mg NETA) tablets are approved for the following indications:

- treatment of vasomotor symptoms and vulvar and vaginal atrophy in women with an intact uterus under NDA 20-907, approval date November 18, 1998 and
- prevention of postmenopausal osteoporosis in women with an intact uterus under NDA 21-103, approval date April 11, 2000

In this submission, Novo Nordisk is seeking an indication for the use of a new lower strength dosage of Activella (0.5 mg E2/0.1 mg NETA), for the prevention of osteoporosis in postmenopausal women with an intact uterus from the Division of Metabolic and Endocrine Products (DMEP). A duplicate submission was also simultaneously submitted to the Division of Reproductive and Urologic Products (DRUP) seeking an indication for the treatment of moderate to severe vasomotor symptoms in postmenopausal women. The sponsor has requested the both DMEP and DRUP coordinate their reviews towards a single approved label by the time of the action goal date.

2.2 Currently Available Treatment for Indications

Activella NDA 20-907, containing 1 mg of E2 and 0.5mg of NETA, is currently approved in women who have a uterus for:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

Besides Activella, the following estrogen-containing products have been approved for the

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prevention of osteoporosis in postmenopausal women.

Estrace (Warner Chilcott)

Femhrt (Warner Chilcott)

Ogen (Pfizer)

Ortho-Est (Sun Pharma Inds)

Ortho-Prefest (Duramed Pharms)

Ortho Tricyclen (Ortho McNeil)

Prefest (King Pharms)

Premarin, Prempro, Premphase (Wyeth)

Alora transdermal patch (Watson Labs)

Climara, ClimaraPro, Menostar transdermal patch (Berlex)

Vivelle transdermal patch (Novartis, Pharms)

The following bis phosphonates are approved for the prevention of osteoporosis

Actonel, Actonel with Calcium (Procter and Gamble)

Boniva (Hoffman-LaRoche)

Fosamax, Fosamax Plus D (Merck)

The following other drugs are approved for the prevention of osteoporosis

Evista (Eli Lilly) -selective estrogen receptor modulator

Forteo (Eli Lilly) - recombinant human parathyroid hormone (1-34)

Fortical (Unigene) - recombinant salmon calcitonin

2.3 Availability of Proposed Active Ingredient in the United States

Estradiol is currently available in the US in tablet form as:

Activella (Novo Nordisk)

Estrace (Warner Chilcott)

Estradiol (Watson, Mylan)

Gynodiol (Novavax)

Estradiol is currently available in the US in a transdermal patch as:

Alora ETS (Watson)

Climara, Climara Pro, Menostar (Berlex)

Estradiol (Mylan)

Vivelle, Vivelle-DOT, CombiPatch (Novartis)

Estradiol is currently available in the US in a topical emulsion as:

Estrasorb (Novavax)

Estrogel (Solvay)

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Estradiol is currently available in the US for vaginal use as:

Estrace Vaginal Cream, (Warner Chilcott)

Estring Vaginal Ring (Pharmacia & Upjohn)

Vagifem (Novo Nordisk)

Norethindrone Acetate is currently available in the US in tablet form as

Activella (Novo Nordisk)

Aygestin (Duramed)

Femhrt, Loestrin 21, Loestrin Fe (Warner Chilcott)

Micorgestin, Micorgestin Fe (Watson)

Norethindrone Acetate is currently available in the US in a transdermal patch as

CombiPatch (Novartis)

2.4 Important Issues With Pharmacologically Related Products

In June 2002 the Women's Health Initiative (WHI) Study reported higher rates of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women during 5 years of treatment with oral conjugated estrogens combined with progesterone relative to placebo¹. As a result of this all estrogen products marketed in the US now include a black box warning suggesting that they be given at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. It is because of this recent guidance from both US and European regulatory authorities that the sponsor has developed this lower strength dosage form.

2.5 Presubmission Regulatory Activity

In a Dec. 2002 meeting with the sponsor, DMEP agreed that Novo Nordisk did not need to conduct an additional 2-year bone mineral density (BMD) study prior to submitting a supplement requesting the approval of lower strength Activella for the prevention of postmenopausal osteoporosis.

2.6 Other Relevant Background Information

Activella low dose was developed for the US and Europe, and an application for marketing of this product was submitted to the EU on Jan. 28, 2006, prior to the submission of this application. The results of the EU application are still pending and it is currently not marketed in any foreign country.

¹ Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. *JAMA*. Vol. 288, No. 3, 2002: 321-333

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3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Activella low dose is a combined hormone replacement therapy product containing 0.5mg of E2 and 0.1mg of NETA per tablet.

3.2 Animal Pharmacology/Toxicology

No new data was submitted. The sponsor instead referenced data submitted and reviewed in the original Activella application NDA 20-907.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data and study reports were submitted electronically for trials EST/PD/4/N+S, ALD-1640 and ALD-1537 (\\Cdsesub1\N22001). For trial KLIM/PD/11/USA, a clinical study report was submitted without any clinical data as this trial had already been reviewed by the agency at the time of the original NDA 20-907 submission.

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4.2 Tables of Clinical Studies

Table 1

Table of Clinical Studies

Study ID	Design ^a	Study Treatments ^b	No. Subjects Entered/Completed	Duration of Treatment
ALD-1537	Randomised, DB, parallel-group, safety & efficacy (vasomotor symptoms) in postmenopausal women	E2 0.5 mg + 0.1 mg NETA	194/177	6 months (24 weeks)
		E2 0.5 mg + 0.25 mg NETA	182/171	
		Placebo	201/160	
ALD-1640	Open, randomised, single-dose, single-centre, three-way, cross-over, relative bioavailability study	E2 0.5 mg + 0.1 mg NETA E2 0.5 mg + 0.25 mg NETA E2 1 mg + 0.5 mg NETA	24 subjects analysed for PK	three in-house periods of 4 nights, separated by three-week wash-out periods
KLIM/FD/8/USA ^c	Randomised, DB, parallel-group, safety & efficacy (vasomotor symptoms) in postmenopausal women	E2 0.25 mg	68/59	3 months (12 weeks)
		E2 0.5 mg	64/57	
		E2 1.0 mg	67/55	
		E2 2.0 mg	68/54	
		Placebo	66/55	
KLIM/FD/11/USA ^c	Randomised, DB, parallel-group, safety & efficacy (osteoporosis) in postmenopausal women	E2 0.25 mg	49/31	26 months
		E2 0.5 mg	47/28	
		E2 1 mg	45/25	
		E2 1 mg + 0.25 mg NETA	44/24	
		E2 1 mg + 0.5 mg NETA	46/20	
		E2 2 mg + 1 mg NETA	48/32	
EST/PD/4/N+S ^c	Randomised, DB, parallel-group, safety & efficacy (osteoporosis) in postmenopausal women	E2 0.5 mg	40/37	24 months
		E2 1 mg	41/35	
		E2 2 mg	42/36	
		Placebo	43/31	
KLIM/FD/7/USA ^c	Randomised, DB, parallel-group, safety & efficacy in postmenopausal women	E2 1 mg	296/212	12 months
		E2 1 mg + NETA 0.1 mg	294/237	
		E2 1 mg + NETA 0.25 mg	291/242	
		E2 1 mg + NETA 0.5 mg	295/234	

a. DB=double-blind

b. all treatments were given orally, once-daily

c. conducted during the Activella[®] clinical development program

4.3 Review Strategy

The indication for the prevention of osteoporosis in postmenopausal women, including trials EST/PD/4/N+S, and KLIM/PD/11/USA, was reviewed by DMEP, whereas the indication for the treatment of moderate to severe vasomotor symptoms in postmenopausal women, including trials ALD-1640 and ALD-1537, were reviewed by Dr. Phill Price and Dr. Sandra Suarez in DRUP. Both divisions collaborated on the final label negotiated with the sponsor.

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4.4 Data Quality and Integrity

Two site inspections were performed for the pivotal trial KLIM/PD/11/USA:

Table 2

Site Inspections for Protocol KLIM/PD/11/USA

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Louis M. Cohen, M.D.	Sarasota, FL	9/15/99	12/6/99	VAI-RR/09864
Maria Greenwald, M.D.	Palm Springs, CA	1/20/00	3/30/00	NAI/010026

Overall, no violations were observed that would affect the reliability or integrity of the data and no follow up action was needed.

4.5 Compliance with Good Clinical Practices

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

4.6 Financial Disclosures

The pivotal trial, study KLIM/PD/11/USA, was previously reviewed by Dr. Zawadzki as part of NDA 21-103 and the financial disclosure information was found to be acceptable.

The supporting efficacy trial, EST/PD/4/N+S, which was not necessary for approval of the indication for prevention of postmenopausal osteoporosis (PMO), was conducted in Norway and Sweden and completed in November 1998 prior to the time line when financial disclosure was required. No financial disclosure information was collected by the sponsor for this study and none was included in this application.

The PK trial, ALD-1640, had only one clinical investigator, Dr. Rohrle in Germany, who submitted financial disclosure information that neither he nor any member of his immediate family had shares or proprietary interest in Novo Nordisk, or received any payments in excess of \$25,000 excluding the costs of running the trial.

The six month trial used to support the indication for the treatment of postmenopausal symptoms, ALD-1537, had financial disclosure information provided for 75/92=82% of the clinical investigators involved in this trial confirming that they nor any member of their immediate families had shares or proprietary interest in Novo Nordisk, or received any payments in excess of \$25,000 excluding the costs of running the trial. The reporting rate was >88% at each trial site except for a single site in France where 9 out of the 12 clinical investigators (75%) did not submit financial disclosure information. This study was reviewed by DRUP for the indication of treatment of vasomotor symptoms associated with menopause, and the reader is

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referred to that review to determine if financial interests may have affected the primary outcome variable in that trial.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Study ALD-1640, a single dose, three-way, cross-over, relative bioavailability study of three oral formulations for hormone replacement therapy in postmenopausal women: 0.5 mg Estradiol + 0.1 mg Norethisterone Acetate [Treatment A, two tablets], 0.5 mg Estradiol + 0.25 mg Norethisterone Acetate [Treatment B, two tablets], and 1.0 mg Estradiol + 0.5 mg Norethisterone Acetate [Treatment C, one tablet] was formally reviewed in DRUP, HFD-580 by Dr. Sandra Suarez. A brief synopsis of this study and the key highlights as they refer to the efficacy and safety of 0.5 mg estradiol + 0.1 mg norethisterone acetate for the prevention of PMO is presented in the appendix.

This study confirmed the relative bioavailability of estradiol, estrone and NETA in all three treatments, as all confidence intervals for the pre-specified concentration dependent endpoints of the pharmacokinetic analysis were within the commonly used acceptance range for bioequivalence (0.8 to 1.25).

Table 3

Study ALD-1640 Pharmacokinetic Analysis

Substance Parameter - Method	Ratio A / C with 90% Confidence Interval	Ratio B / C with 90% Confidence Interval
Estradiol (E2) baseline corrected		
AUC(0-t) - Mixed (ln)	95.75% (89.39%, 102.56%)	98.01% (91.49%, 104.97%)
C _{max} - Mixed (ln)	101.18% (90.12%, 113.59%)	95.59% (85.14%, 107.31%)
Estrone (E1) baseline corrected		
AUC(0-t) - Mixed (ln)	97.70% (90.14%, 105.87%)	100.06% (92.32%, 108.43%)
C _{max} - Mixed (ln)	98.34% (90.80%, 106.49%)	99.50% (91.88%, 107.75%)
Norethindrone (NET)		
AUC(0-∞) - Mixed (ln)	102.60% (94.68%, 111.17%) ^a	96.70% (89.39%, 104.59%)
C _{max} - Mixed (ln)	113.12% (106.23%, 120.45%) ^a	98.30% (92.31%, 104.67%)

^a concentration dependant endpoints corrected for dose

The pharmacokinetics of estradiol and estrone were not influenced by the dose of norethisterone acetate within the dose range administered in this study, i.e. 0.2 to 0.5mg, and there is dose adjusted proportional pharmacokinetics of NET within the dose range administered in this study, i.e. 0.2 to 0.5mg.

5.2 Pharmacodynamics

There was no new pharmacodynamic data submitted with bioequivalence study ALD-1640. All previously submitted pharmacodynamic information has been previously reviewed and found acceptable. Changes in markers of bone turnover were included as secondary endpoints in trials EST/PD/4/N+S, and KLIM/PD/11/USA and discussed in the review of these trials in the appendix.

5.3 Exposure-Response Relationships

There were no new exposure-response relationships in this submission.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Prevention of postmenopausal osteoporosis (PMO)

6.1.1 Methods

There were two efficacy trials submitted in this application for this indication. The pivotal trial, KLIM/PD/11/USA, was found acceptable and used to support the new labeling changes. This trial had been originally reviewed by Dr. Joanna Zawazdki (medical officer) and Japo Choudhury (statistician) during the initial submission of NDA 21-103. The new supportive trial, EST/PD/4/N+S, was reviewed by this medical officer and Cynthia Liu (statistician), but the study design was found to be flawed and did not allow extrapolation of data to current standard of care treatment of PMO. Therefore, this medical reviewer does not recommend including study EST/PD/4/N+S as part of the current labeling changes for the PMO indication.

6.1.2 General Discussion of Endpoints

Fracture reduction is the gold standard endpoint for treatment of osteoporosis. Changes in bone mineral density (BMD), bone biomarkers and bone biopsies provide supportive evidence of efficacy. BMD has been used as a primary efficacy endpoint as long as the newly formed bone was of normal quality. In the case of estrogens, BMD has been shown to be an effective surrogate for fracture reduction and is considered an acceptable endpoint for prevention of PMO. In both studies (KLIM/PD/11/USA) and (EST/PD/4/N+S) the primary efficacy endpoint was change in lumbar spine BMD compared to placebo.

6.1.3 Study Design

KLIM/PD/11/USA was a double-blind, randomized, placebo-controlled, parallel-group, 26 month study in healthy postmenopausal women 45 years of age or older with an intact uterus

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performed in the US. Women were one to 5 years post menopause and had a BMD score less than two standard deviations below the young adult normal mean (i.e. $>0.827\text{gm/cm}^2$ for _____ or $>0.940\text{gm/cm}^2$ for _____). A total of 737 women were screened, 327 were randomized, and 189 completed the study. Exclusion criteria included but were not limited to: MI in the last 6 months, history of stroke, thrombophlebitis or thromboembolic disorder, heavy cigarette smoker (>20 cigarettes per day), $>30\%$ above ideal body weight, systolic BP $\geq 160\text{mm Hg}$ or diastolic BP $\geq 100\text{mm Hg}$, evidence of nontraumatic osteoporotic fracture within the past 2 years, chronic treatment with steroids, endometrial hyperplasia or endometrial thickness $>6\text{mm}$.

Subjects were randomly assigned to one of seven treatment groups:

1. 2 mg E2 and 1.0 mg NETA
2. 1 mg E2 and 0.5 mg NETA
3. 1 mg E2 and 0.25 mg NETA
4. 1 mg E2 alone
5. 0.5 mg E2 alone
6. 0.25 mg E2 alone
7. Placebo

All subjects were administered calcium supplementation (1000mg/day) as instructed by the investigator. In general, discontinuation rates were similar for the combination treatment groups (33 to 40%) compared to the placebo group (40%). They were somewhat higher for the estrogen alone groups (44 to 56%), which had a higher frequency of endometrial hyperplasia and bleeding.

Medical Officer's comment-

The other efficacy trial, EST/PD/4/N+S was a double-blind, randomized study in healthy postmenopausal women 45 years of age or older. All women were hysterectomised, and it included perimenopausal (FSH >20 IU/L & ≤ 40 IU/L) in addition to postmenopausal (FSH >40 IU/L). In addition, there was no calcium or Vitamin D supplementation in this trial. Since the study was performed in Sweden and Norway which do not routinely supplement dairy products with Vitamin D, it is likely that many of these patients were calcium deficient at baseline.

Since

- 1) hysterectomized women would not be normally treated with a combination estrogen progestin drug product such as 0.5 mg E2 and 0.1 mg NETA,*
- 2) there is no current indication to treat perimenopausal women for the prevention of PMO, and*
- 3) current therapy in the US recommends calcium and vitamin D supplementation prior to treatment of PMO with medications*

it is this medical officer's conclusion that study results from EST/PD/4/N+S cannot be used to support current treatment in the US and these data should not be used in

labeling. Therefore, efficacy findings from this trial were not included in section 6.1.4 but can be found in the appendix.

6.1.4 Efficacy Findings

Medical Officer's comment-

The 0.5mg E2/0.1 mg NETA formulation, which was submitted for approval in this submission, was not directly tested in a 2 year BMD efficacy trial. Data from KLIM/PD/11/USA will be presented in the efficacy findings that support 0.5mg of E2 alone is statistically-better than placebo in maintaining LS BMD. In addition, data from this same trial will show that at a constant estrogen concentration, increasing the NETA level results in slightly better LS BMD efficacy. Therefore, the addition of 0.1mg NETA to 0.5mg E2 would be expected to increase LS BMD more than 0.5mg E2 alone, and to be statistically better than placebo.

BMD values at the lumbar spine increased with increasing estrogen dosage, while BMD decreased in women in the placebo group. Although, the study was not designed to evaluate differences between active-treatment groups, it did appear to show a dose-related trend in increase in LS BMD with respect to estrogen dosage. The modified ITT, LOCF analysis of the percent change from baseline for BMD of lumbar spine showed that the placebo group had a mean 2.12% decrease in BMD (Table 4 and Figure 1). The 0.5mg E2 treatment group showed a mean increase of 2.26%, in BMD after 2 years, which was statistically significant, $p < 0.001$, 95% confidence intervals of 2.89 to 5.86. The net difference from placebo was $2.26 - (-2.12\%) = 4.38\%$.

The Per Protocol analyses at 26 months gave similar results for LS BMD. It showed a mean decrease of 2.04% in the placebo group compared to an increase of 2.21% in the 0.5mg E2 treatment group, for a net difference of 4.25%, $p < 0.001$.

Table 4

**Study KLIM/PD/11/USA-Primary Efficacy Analysis: LS BMD
 (Data taken from sponsor's Table 8.2.1.1 Clinical Trial Report)**

TABLE 8.2.1.1. BMD OF LUMBAR SPINE: % CHANGE FROM BASELINE - LOCF

Treatment	N	Mean	SD	Median	Range	P-value	Compared to Placebo	
							Difference	95 % CI
Placebo	37	-2.12	2.860	-2.06	-7.59 - 4.24			
1 mg E ₂ + 0.25 NETA	37	3.54	3.679	3.64	-5.40 - 10.10	<0.001	5.66	(4.18, 7.14)
1 mg E ₂ + 0.5 NETA	37	3.80	3.034	3.78	-2.69 - 9.06	<0.001	5.92	(4.44, 7.40)
0.25 mg E ₂	37	0.39	2.927	0.56	-5.18 - 9.21	0.001	2.51	(1.09, 3.92)
0.5 mg E ₂	31	2.26	2.760	2.44	-2.82 - 8.48	<0.001	4.37	(2.89, 5.86)
1.0 mg E ₂	37	2.76	2.877	2.95	-3.84 - 8.94	<0.001	4.88	(3.46, 6.30)
2.0 mg E ₂ + 1.0 NETA	42	4.99	3.750	4.98	-4.12 - 15.52	<0.001	7.11	(5.74, 8.48)

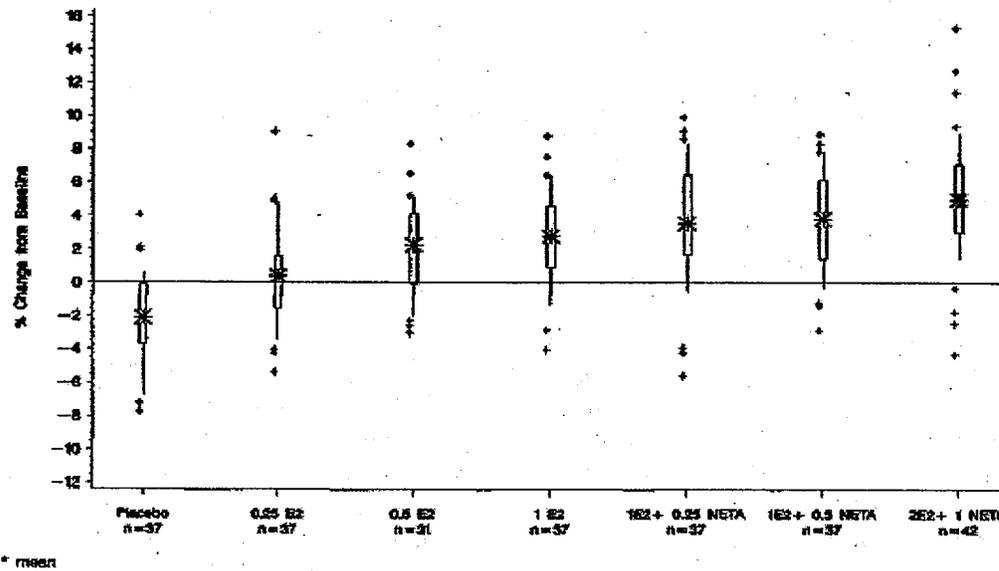
LOCF: Last Observation Carried Forward; P-values are from Analysis of Variance

BMD values at the lumbar spine increased with increasing NETA dosage at a constant estrogen dose of 1mg e.g. 0mg NETA +2.76%, 0.25mg NETA +3.54%, 0.5mg NETA +3.80% (see Table 4).

Figure 1

**Study KLIM/PD/11/USA-Primary Efficacy Analysis: LS BMD
 (Data taken from sponsor's Figure 8.2.1.1A Clinical Trial Report)**

FIGURE 8.2.1.1A. BMD OF LUMBAR SPINE: % CHANGE FROM BASELINE - LOCF



Statistically significant changes from baseline were also seen for the secondary endpoints BMD at the proximal femur.

Treatment site	N	Mean % BMD	SD	P-value	Net difference	95% CI
Femoral neck						
Placebo	37	-2.26	3.4			
0.5mg E2	30	0.26	2.9	<0.007	2.52	(0.070, 4.34)
Femoral trochanter						
Placebo	37	-1.95	4.3			
0.5mg E2	30	1.74	4.1	<0.002	4.48	(2.26, 6.70)

Compared to the highest percentage of subjects who showed an increase in BMD above baseline ($\geq 0\%$ BMD) in the highest combination dose group i.e. 2mg E2 + 1.0 NETA, the effect seen with 0.5mg of E2 was intermediate but still substantially greater than seen in the placebo groups (see Table 6).

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Treatment	Lumbar Spine		Femoral Neck		Femoral Trochanter	
	N	%	N	%	N	%
Placebo	37	22	37	27	42	32
0.5mg E2	31	74	30	57	36	67
2mg E2 + 1.0 NETA	42	91	42	76	44	83

These data cannot be used to conclude that some patients may not be responding to E2, because even subjects who had a decrease in BMD at specific sites may have observed an even greater decrease in BMD in the absence of treatment with estrogen.

Urinary bone markers were generally also supportive of the BMD increases seen with estrogen. Urinary pyridinoline, and deoxypyridinoline have been used to estimate bone turnover. The urinary concentrations of pyridinoline, and deoxypyridinoline decreased in the active control groups, consistent with estrogen acting as an anti-resorptive agent, whereas bone specific alkaline phosphatase increased in all treatment arms compared to baseline. The increase, a measure of bone turnover, was smaller in the active treatment arms, also consistent with estrogen acting as an anti-resorptive agent.

Bone Marker	Treatment group	Number	Median % Change from Baseline
Bone Specific Alkaline Phosphatase (ng/mL)	Placebo	41	114
	0.5mg E2	36	90
Urinary Pyridinoline (nmol/mmol)	Placebo	40	-6
	0.5mg E2	35	-22
Urinary Deoxypyridinoline (nmol/mmol)	Placebo	40	-9
	0.5mg E2	35	-22

6.1.5 Clinical Microbiology

No clinical microbiology data was included in this submission.

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6.1.6 Efficacy Conclusions

- 1) There was a statistically significant increase in lumbar spine, proximal femur and femoral trochanter BMD observed at 2 years in postmenopausal women treated with 0.5mg E2 relative to placebo.
- 2) Urinary bone markers findings were supportive of the BMD increases seen with estrogen.
- 3) BMD values at the lumbar spine increased with increasing NETA dosage (0 to 0.5mg) at a constant E2 dose of 1mg.
- 4) A combination drug product containing 0.5mg E2 and 0.1mg NETA would be expected to significantly increase LS BMD in postmenopausal women compared to placebo.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

No combined safety analysis was included in this submission. Treatment for prevention of PMO with 0.5mg of E2 for up to two years was assessed in trials KLIM/PD/11/USA, and EST/PD/4/N+S. No new safety concerns were identified in these studies. Detailed safety analyses of these individual studies are included in the appendix.

The clinical safety of treatment with 0.5mg E2/0.1mg NETA for up to 6 months was assessed in trials ALD-1537. This trial also confirmed that 0.1mg of NETA was sufficient to prevent the endometrial hyperplasia seen with 0.5mg E2 alone. No new safety concerns were identified in this study. A detailed safety analysis of this study is included in the appendix.

7.1.1 Deaths

KLIM/PD/11/USA

One subject in the 1mg E2 + 0.5mg NETA group died from a metastatic adenocarcinoma two months after withdrawing from the study. She had received 439 days of therapy before the study medication was stopped. A tentative diagnosis of ovarian carcinoma was made but it was not confirmed because an autopsy was not performed. The clinical investigator deemed this adenocarcinoma was unlikely to be due to the study drug.

EST/PD/4/N+S

One subject in the 1mg E2 group died with ovarian carcinoma. She had a family history of two sisters with ovarian cancer. It is likely that this was unrelated to the study medication.

ALD-1537

One subject in the placebo group died from a fatal myocardial infarction during the trial. No deaths were reported in the 0.5mg E2 + 0.1mg NETA group.

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7.1.2 Other Serious Adverse Events

KLIM/PD/11/USA

There were 18 women with 23 serious adverse events reported in the combined E2 treatment groups (18/279=6.5%) compared to only one in the placebo group (1/48= 2.1%). In the 0.5mg E2 alone treatment group there were three women (3/44=6.8%) with four serious adverse events (e.g. viral infection, back pain, uterovaginal prolapse, and cholelithiasis), which were all unlikely or at most possibly related to the study drug.

EST/PD/4/N+S

There were 17 women with 21 serious adverse events reported in the study, with an equal distribution across treatment groups (e.g. placebo 4/43=9%, 0.5mg E2 4/40=10%, 1mg E2 4/41=10% and 2mg E2 5/42=12%). In the 0.5mg E2 alone treatment group there were four serious adverse events (e.g. accidental injury, gastroenteritis, hyperparathyroidism and varicose vein), which were all unlikely to be related to the study drug.

ALD-1537

There were 15 women with 17 serious adverse events reported in this study; 6/182=3.3% in the ALD 0.25 group (e.g. breast cancer, pancreatic mass/carcinoma, pelvic pain, salpingitis, myalgia and mechanical complication of implant), 5/194=2.6% in the ALD 0.1 group (e.g. intervertebral disc disorder, depression/concussion, dizziness, ankle fracture and benign breast neoplasm) and 4/201=2.0% in the placebo group (e.g. fatal myocardial infarction, muscle rupture, cholelithiasis and transient ischemic attack). Only the case of breast cancer in the ALD 0.25 group was considered by the sponsor to be possibly related to the study medication and this will be discussed in more detail under Breast Adverse Events in section 7.1.3.2.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Dropouts

KLIM/PD/11/USA

Six women had serious adverse events that resulted in withdrawal from the study (see sponsor's data Table 9.2.2, KLIM/PD/11/USA Clinical Study Report).

- placebo group
 - endometrial hyperplasia
- E2 alone groups
 - uterovaginal prolapse
 - malignant breast neoplasm and
 - pituitary neoplasm
- E2 + NETA combination treatment groups
 - endometriosis and
 - metastatic adenocarcinoma

Only the cases of endometrial hyperplasia in the placebo group and breast neoplasm in the E2 alone group were deemed possibly related to the study drug by the clinical investigator.

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Additional nonserious adverse events that lead to the discontinuation of patients in the treatment groups were

- placebo group
 - breast pain
 - endometrial hyperplasia
 - hot flashes
 - depression/emotional lability
- E2 alone groups
 - post menopausal bleeding
 - breast pain
 - endometrial hyperplasia
 - hot flashes
 - abdominal pain
 - weight gain
 - depression/emotional lability
- E2 + NETA combination treatment groups
 - post menopausal bleeding
 - breast pain
 - hot flashes
 - abdominal pain
 - depression/emotional lability
 - back pain/Tarlov's cyst

EST/PD/4/N+S

Twenty women had adverse events that resulted in withdrawal from the study (see sponsor's data Table 9-4, Clinical Study Report).

- placebo group 10/43=23%
 - hot flushes (6)
 - weight increase
 - cystocele
 - diverticulitis
 - breast fibroadenosis
- 0.5mg E2 1/40=3%
 - hypertonia
- 1mg E2 5/41=12%
 - Ovarian cancer
 - Weight increase
 - Infection in umbilical region
 - Reduced libido
 - Leucorrhoea
- 2mg E2 4/42=10%
 - Facial edema
 - Weight increase

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- Vaginitis
- Fatigue

Only the cases of hot flushes, weight increase, facial swelling, leucorrhea, vaginitis and reduced libido were considered possibly or probably related to the study drug by the clinical investigator.

ALD-1537

The incidence of withdrawal was higher in the placebo group (20%) than both the ALD 0.1 (9%) and ALD 0.25 (6%) treatment groups. The major reason for the difference in withdrawal rate was the higher incidence of ineffective therapy in the placebo group (8%) compared with the treatment groups, ALD 0.1 (2%) and ALD 0.25 (1%).

A total of 31 patients withdrew from the study because of adverse events, 4 subjects (2%) in the ALD 0.25 group and 11 subjects (6%) in the ALD 0.1 group, and 16 subjects (8%) in the placebo group.

ALD 0.25

back pain, upper abdominal pain, vaginal hemorrhage and pain in extremity
nervousness
paresthesias
alopecia

ALD 0.1

benign breast neoplasm
vaginal hemorrhage and endometrial thickening
hypertension
intervertebral disc disorder
groin pain, pain in extremity, hand and leg stiffness
fluid retention, urinary retention, and malaise
pain in extremity
abdominal pain, nausea, diarrhea, dyspepsia, and abnormal LFT
headache, dizziness, disturbance in attention
concussion and depression
mental impairment

Placebo

endometrial thickening
vaginal hemorrhage
hot flashes
hypertension
hypertension, depressed mood, and arthralgia
palpitations
shoulder pain and muscle rupture
gastric disorder
abdominal pain, constipation and dyspepsia

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abdominal pain, cholelithiasis
nausea and abdominal pain
tinnitus
transient ischemic attack
weight increase
migraine
migraine

In summary the type of adverse events leading to study withdrawal were not unexpected in postmenopausal women on hormone replacement therapy.

7.1.3.2 Breast Adverse Events

KLIM/PD/11/USA

There were two cases of breast cancer deemed by the clinical investigators as possibly or probably related to the study treatment: a malignant breast neoplasm in one patient treated with a higher dose of E2 (i.e. 1.0mg E2 alone for 729 days) and in one patient treated with a lower dose of E2 (i.e. 0.25mg E2 alone for 495 days). In addition to these 2 cases of malignant breast cancer there were 6 other non serious clinically significant mammography results in the E2 or E2 + NETA treatment groups compared to none in the placebo group.

E2 alone

1mgE2 (49 y/o day 720)

0.25mg E2 (57 y/o day 362)

E2 + NETA

2mgE2+ 1mg NETA (47 y/o day 477)

1mgE2+0.25mg NETA (56 y/o day 216, 52 y/o day 729)

1mgE2 + 0.5mg NETA (58y/o day 364)

While these data suggest that estrogens may contribute to abnormal breast findings including cancer, the number of patients in this study is too small to come to any clear conclusions. Recent findings from the Women's Health Initiative, which has enrolled over 160,000 women over the past 15 years, suggested that unopposed estrogen was not associated with an increased risk of breast cancer but that the progesterone component of combined hormone therapy was important at increasing the risk. In study KLIM/PD/11/USA there were more abnormal finding in patients on combined therapy but the two malignancies were in patients taking estrogen alone. The inconsistency between this study and the WHI results shows how difficult it is to draw credible conclusions from studies with a small number of patients.

EST/PD/4/N+S

No cases of abnormal breast findings were reported in the E2 treatment groups. There was one case of breast fibroadenosis which was reported in the placebo group which led to withdrawal of the patient from the study.

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Clinically important symptoms relating to the breast (breast discomfort, breast pain and tenderness) were each reported by $\leq 2\%$ of subjects treated with Activelle (0.5mg E2/0.1mg NETA), which was comparable with the placebo group. One subject in the ALD 0.25 treatment group was diagnosed with breast cancer after being treated for 173 days during the course of the trial. She had received hormone replacement products for 13 years prior to being enrolled in this study. So it is unlikely that the study drug was solely responsible for this adverse event. Mammographs were carried out on a subpopulation of 255 postmenopausal women from Nordic countries: Norway, Sweden, Denmark and Finland. Mammograms were performed prior to the start of treatment and after 6 months, using the same equipment at each assessment. The baseline mammogram was made during the screening period (it was also acceptable to use mammograms taken up to six months prior to trial entry) and the follow up mammogram was performed at the last visit or after at least five months of treatment. All patients who used systemic hormone replacement therapy up to two months prior to the screening mammogram were excluded from the analysis. At screening, mean breast density assessed by digitized quantification was 22.5%, 21.3% and 20.7% for ALD 0.25, ALD 0.1 and placebo, respectively. After 24 weeks of treatment the values were 23.9%, 21.1% and 21.4%, respectively. No overall treatment differences were detected between the treatment groups and placebo. Visual assessment according to the Wolfe classification and the percentage scale showed no increase in breast density after 24 weeks of treatment with Activelle (0.5mg E2/0.1mg NETA). While this 6 month study showed no definite evidence of an increase in breast cancer risk or breast disease compared to placebo with this low dose estrogen formulation, it is not possible to extend these data to longer durations of therapy.

7.1.3.3 Endometrial Disorders

KLIM/PD/11/USA

Endometrial disorders were seen in one placebo patient (1/48=2.1%, hyperplasia), one patient with 1mg E2 + 0.25mg NETA (1/49=2.0%, endometriosis), one patient with 1mg E2 alone (1/46=2.2%, hyperplasia), one patient with 0.25mg E2 alone (1/45=2.2%, hyperplasia and endometriosis) and in one patient with 2mg E2 + 1.0mg NETA (1/48=2.1%, endometrial disorder unspecified). Again, the small number of patients in each treatment group makes it difficult to draw any clear conclusions from these data. However, endometrial biopsies confirmed the protective effect of NETA on the endometrium as there were no cases of endometrial hyperplasia with combined continuous treatment with NETA doses of 0.25mg or higher. In the 1mg E2 alone group there were 9 out of 32 (28%) positive biopsies. In the 0.5 mg E2 alone group there was 1 out of 30 (3%) positive biopsies. There were no positive biopsies in the 0.25 mg E2 alone group. There was 1 out of 35 (3%) positive biopsies in the placebo group which was unexpected and for which the sponsor could not provide a clear explanation. The protective effect of NETA on the endometrium was also observed in measurements of the mean or median increase in endometrial thickness between the treatment groups although individual patient data was not provided.

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EST/PD/4/N+S

This study comparing unopposed estrogen to placebo enrolled only hysterectomized women.

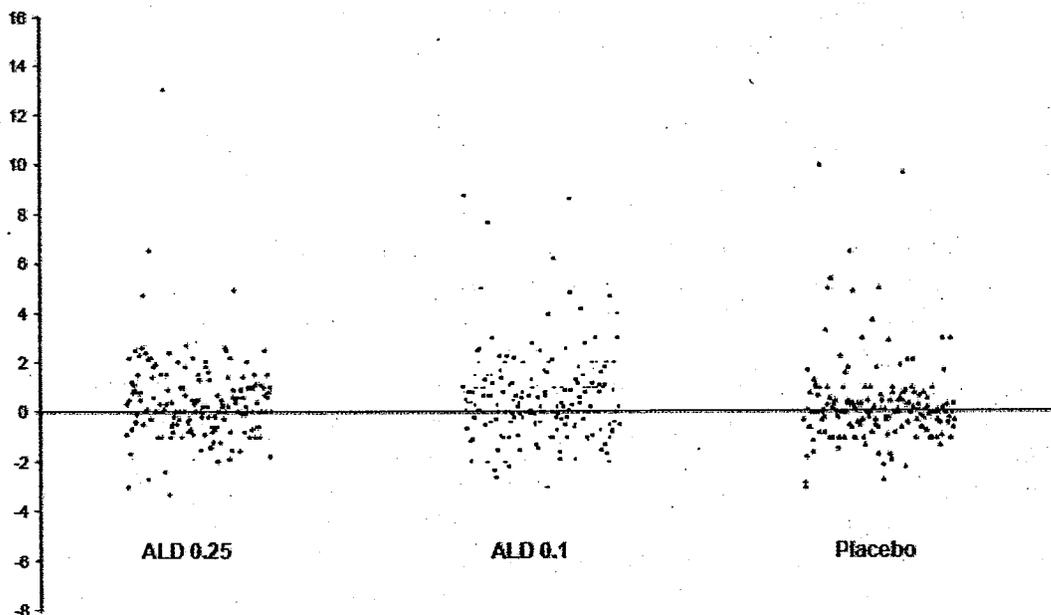
ALD-1537

One major safety concern with estrogen and progesterone drug products is whether there is sufficient progesterone present to prevent estrogen induced endometrial hyperplasia. Study ALD-1537 was the only one submitted which looked at women treated with the to-be-marketed 0.5mg E2/0.1mg NETA formulation. All subjects tested had normal Papanicolaou smear test findings at screening. At week 24 one subject each in the ALD 0.1 group (of 183; 1%) and the placebo group (of 178; 1%) had abnormal smear test findings. The incidence of endometrial thickening, described as ≥ 5 mm at the last visit, was 6% (11 subjects) in the ALD 0.25 group, 10% (19 subjects) in the ALD 0.1 group and 6% (8 subjects) in the placebo group. The distribution of endometrial thickness changes, last visit thickness minus screening visit thickness, between the three treatment groups was similar and changes primarily ranged between -2 mm and +2 mm with some cases occurring outside (above and below) these values (see Figure 2).

Figure 2

ALD-1537 Summary of Endometrial Thickness Changes
(last visit thickness minus screening visit thickness)
(Data taken from sponsor's Figure 10-1, Clinical Trial Report)

Change (mm)



The mean endometrial thickness values during the screening visit and the final visit are summarized in Table 8. There was a slight increase in the mean endometrial thickness in all treatment groups over the course of the trial, increasing from 2.23mm to 2.65mm in the ALD 0.25 group, from 2.29mm to 2.87mm in the ALD 0.1 group and from 2.30mm to 2.56mm in the

placebo group. The mean endometrial thickness during the screening visit as well as at the end of the trial was always within the normal postmenopausal range (< 5 mm) and is consistent with an adequate amount of progestin in this combination drug product to prevent estrogen induced endometrial hyperplasia.

Table 8

**ALD-1537 Summary of Endometrial Thickness
 (Data taken from sponsor's Table 10-4 Clinical Trial Report)**

Table 10-4 Summary of Endometrial Thickness (mm) (Safety Population)

Treatment		Week 0	Week 24
ALD 0.25	Number	181	173
	Mean ± SD	2.23 ± 1.07	2.65 ± 1.64
	Median	2.00	2.40
	Range	0.00 – 4.90	0.00 – 13.00
ALD 0.1	Number	194	185
	Mean ± SD	2.29 ± 1.00	2.87 ± 1.82
	Median	2.10	2.50
	Range	0.00 – 4.80	0.00 – 12.00
Placebo	Number	200	177
	Mean ± SD	2.30 ± 1.06	2.56 ± 1.64
	Median	2.00	2.20
	Range	0.00 – 7.30	0.00 – 11.00

Cross-reference EOT Table 107

Endometrial biopsies were not a protocol-planned procedure conducted in the ALD-1537 trial. However, at the discretion of the investigators, 5 patients underwent endometrial biopsies and all results were negative with regard to endometrial abnormalities. See Dr. Price's review for a more detailed analysis of the risk of endometrial hyperplasia with the to-be-marketed formulation.

7.1.3.4 Cardiovascular Adverse Events

The WHI study reported higher rates of myocardial infarction, stroke, pulmonary emboli and deep venous thrombosis in postmenopausal women during 5 years of treatment with oral conjugated estrogens compared to placebo.

KLIM/PD/11/USA

There was no increase in cardiovascular events in the 0.5mg E2 group compared to placebo reported in this 24-month study.

EST/PD/4/N+S

There was no increase in serious cardiovascular events reported in this 24-month study. One patient in the 0.5mg E2 group had an adverse event of postural hypertension and one patient in the 2mg E2 group had an adverse event of hypertension.

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ALD-1537

There was no increase in cardiovascular events in the E2/NETA groups in this 6-month study compared to placebo. Cardiovascular events occurred in 2% of subjects treated with ALD 0.25, 4% of subjects treated with ALD 0.1, and 6% of subjects in the placebo group. One patient died of a myocardial infarction in the placebo group. There was one adverse report of hypertension in the ALD 0.1 group compared to two reports of hypertension in the placebo group. There was one report of a transient ischemic attack in the placebo group. Both Activelle _____ combinations showed neutral to favorable changes in lipid and lipoprotein, blood clotting parameters and glucose metabolism over the observation period. No mean changes in weight or blood pressure were reported during the 24-week trial period in the Activelle _____ treatment groups. While this 6-month study showed no evidence of an increase in cardiovascular events or worsening of potential markers for cardiovascular disease compared to placebo with low dose estrogen formulations, it is not possible to extend these data to longer durations of therapy. In addition, since this study excluded women with hypertension, active cardiovascular disease, or thromboembolic disorders, the risk associated with treating such patients with low dose estrogen preparations was not assessed.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

KLIM/PD/11/USA

Treatment emergent AEs reported by $\geq 5\%$ of the women in any group are summarized by system-organ class in Table 9 in the appendix. The incidence of AEs seen with 0.5mg E2 (n=11, 23%) was similar to the placebo group (n=11, 25%). AEs categorized as reproductive disorders were the most commonly reported events with breast pain seen more commonly in the continuous combined treatment groups, and endometrial hyperplasia/post-menopausal bleeding seen primarily in the E2 alone treatment groups. AEs occurring in at least 2 more patients in the 0.5mg E2 group compared to the placebo group were seen in order of occurrence as abdominal pain (5 vs. 0), dizziness, flatulence, back pain and rash (4 vs. 0, 1, 2, 2, respectively), and postmenopausal bleeding (3 vs. 0). These AEs were not unexpected for subjects receiving estrogen replacement therapy.

EST/PD/4/N+S

Adverse events reported by $\geq 5\%$ of the women in any treatment group are presented in Table 15 in the appendix. The incidence of AEs seen with 0.5mg E2 (n=30, 75%) was slightly lower than seen in the placebo group (n=36, 84%). AEs that were the more common in the placebo group were hot flashes (33% vs. 5 to 7%), sinusitis (12% vs. 0 to 5%) and ovarian cyst (7% vs. 0%), whereas only back pain was more common in all the estrogen treatment groups compared to placebo (5% to 12% vs. 0%). These AEs were not unexpected for subjects receiving estrogen replacement therapy.

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ALD-1537

Adverse events reported by $\geq 5\%$ of the women in any treatment group are presented in Table 23 in the appendix. The incidence of AEs seen with 0.1mg NETA (n=147, 76%) was slightly higher than seen in the placebo group (n=139, 70%), with the following AEs seen more commonly in both NETA treatment groups compared to placebo e.g. vaginal hemorrhage (22 to 26% vs. 12%), headache (22 to 26% vs. 19%), nasopharyngitis (19 to 21% vs. 18%), back pain (6 to 10% vs. 4%), endometrial thickening (6 to 10% vs. 4%), and pharyngeal pain (4 to 5% vs. 3%) These AEs were not unexpected for subjects receiving estrogen replacement therapy.

7.1.6 Less Common Adverse Events

KLIM/PD/11/USA, EST/PD/4/N+S and ALD-1537

All AEs were described in section 7.1.5 Common Adverse Events.

7.1.7 Laboratory Findings

KLIM/PD/11/USA, EST/PD/4/N+S and ALD-1537

No clinically significant changes in mean values for clinical chemistry, hematology and urinalysis were seen in these studies.

7.1.8 Vital Signs

KLIM/PD/11/USA, EST/PD/4/N+S and ALD-1537

No clinically significant changes in mean values for vital signs were seen in these studies.

7.1.9 Electrocardiograms (ECGs)

No ECG data was submitted in these studies.

7.1.10 Immunogenicity

No immunogenicity data was submitted in this NDA.

7.1.11 Human Carcinogenicity

The current Activella label states that:

Long-term continuous administration of estrogen, with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer.

No new carcinogenicity data was included in this NDA.

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7.1.12 Special Safety Studies

No special safety studies were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Estrogen withdrawal in women is associated with estrogen break through bleeding, vasomotor symptoms, urogenital atrophy and osteoporosis. No new information on withdrawal phenomena was included in this submission.

There is no abuse potential with estrogen or progesterone drug products.

7.1.14 Human Reproduction and Pregnancy Data

Activella is currently labeled not to be used during pregnancy although there appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. No new information on human reproduction and pregnancy data was included in this submission.

7.1.15 Assessment of Effect on Growth

No new information on the effect of estrogens or progestins on growth was included in this submission.

7.1.16 Overdose Experience

The current label for Activella states that serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. In addition, overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding in females. No new information about overdosage was included in this NDA submission.

7.1.17 Postmarketing Experience

No information on postmarketing experience was included in this submission.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The pivotal trial KLIM/PD/11/USA and the two supporting trials EST/PD/4/N+S and ALD-1537 were used to evaluate the safety of Activella.

7.2.1.1 Study type and design/patient enumeration

KLIM/PD/11/USA was a 26-month, double-blind, randomized, placebo-controlled, parallel group study in healthy postmenopausal women 45 years of age or older with an intact uterus performed in the US. Women were one to 5 years post menopause and had a BMD score less than two standard deviations below the young adult normal mean (i.e. $>0.827\text{gm/cm}^2$ for or $> 0.940\text{gm/cm}^2$ for _____). A total of 737 women were screened, 327 were randomized, and 189 completed the study. Exclusion criteria included but were not limited to: MI in the last 6 months, history of stroke, thrombophlebitis or thromboembolic disorder, heavy cigarette smoker (>20 cigarettes per day), $> 30\%$ above ideal body weight, systolic BP $\geq 160\text{mm Hg}$ or diastolic BP $\geq 100\text{mm Hg}$, evidence of nontraumatic osteoporotic fracture within the past 2 years, chronic treatment with steroids, endometrial hyperplasia or endometrial thickness $> 6\text{mm}$.

EST/PD/4/N+S was a 24-month, double-blind, randomized, placebo-controlled, parallel-group study in healthy postmenopausal women 45 years of age or older performed in Norway and Sweden. All women were hysterectomised, and perimenopausal (FSH >20 IU/L & ≤ 40 IU/L) or postmenopausal (FSH >40 IU/L). 58 (35%) were oophorectomised, of whom 24 (14%) had a bilateral oophorectomy. The mean age at time of oophorectomy ranged from 42.1 to 48.0 years and the mean time since oophorectomy ranged from 2.0 to 7.5 years (median 2 to 3 years). BMD was not a specific entry criteria, but patients with frank osteoporosis were excluded from the study. Baseline BMD score measured by dual energy x-ray absorptiometry (DEXA, lunar _____ equipment) ranged from 0.842 to 1.584gm/cm^2 . A total of 171 women were randomized, 166 were exposed to study drugs (123 in Norway and 43 in Sweden) and 139 completed the study. Exclusion criteria included but were not limited to: untreated cardiac disease, concomitant use of lipid lowering agent, history of stroke, deep venous thrombosis or thromboembolic disorder, diastolic BP $> 90\text{mm Hg}$, chronic treatment with steroids, and known, suspected or past history of carcinoma of the breast.

ALD-1537 was a 6-month, double-blind, randomized, multi-centre, multi-national, placebo-controlled, parallel-group study in postmenopausal women 45 to 65 years of age performed at 77 sites in 10 different European countries. Women had to have a minimum of 7 moderate to severe hot flashes per day or 50 moderate to severe hot flashes per week during a 2 week run-in period. A total of 793 subjects were screened of which 577 were randomized to receive trial medication (194 received ALD 0.1, 182 received ALD 0.25, 201 received placebo) and 508 completed the study. Exclusion criteria included but were not limited to: heavy smoking (>20 cigarettes a day),

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deep venous thrombosis or thromboembolic disorder, systolic BP \geq 160mm Hg, diastolic BP \geq 100mm Hg, chronic treatment with steroids, and known, suspected or past history of carcinoma of the breast.

7.2.1.2 Demographics

KLIM/PD/11/USA-There were no significant differences in baseline demographic characteristics among the treatment groups. The women were primarily white (range 83 to 98%), had a mean age of 53 years (range 52.3 to 53.5 years), averaged 3 years post menopause (range 2.5 to 3.1 years). The treatment groups had similar mean baseline LS BMD of 1.05 to 1.11g/cm² and low mean rates of previous hormone replacement therapy (4.2 to 8.7%).

EST/PD/4/N+S- There were no differences in baseline demographic characteristics among the treatment groups with respect to age (mean 49 to 50 years, range 44 to 55 years), time since hysterectomy (mean 3.4 to 4.5 years, SD 3.2 to 4.8 years), and baseline LS BMD (mean 1.10 to 1.20g/cm², range 0.84 to 1.58 g/cm²). There were somewhat fewer subjects status post oophorectomy in the placebo group compared to the E2 treatment groups (e.g. placebo 11 (26%), 0.5mg E2 14 (35%), 1mg E2 16 (39%) and 2mg E2 17 (41%), but there was no clear difference for patients status post bilateral oophorectomy between the groups (e.g. placebo 6 (14%), 0.5mg E2 5 (13%), 1mg E2 9 (22%) and 2mg E2 4 (10%).

ALD-1537-There was no difference in baseline demographic characteristics among the treatment groups with respect to age (mean 55 to 56, range 44 to 65 years), race (95 to 96% Caucasian), and time since last menses (69 to 72% had their last menstrual period at between 2 to 10 years previously).

7.2.1.3 Extent of exposure (dose/duration)

KLIM/PD/11/USA- The cumulative exposure to each treatment was as follows: placebo, 877.3 months; 1 mg E2 + 0.25 mg NETA, 931.7 months; 1 mg E2 + 0.5 mg NETA, 903.8 months; 0.25 mg E2 alone, 871.7 months; 0.5 mg E2 alone, 815.5 months; 1 mg E2 alone, 822.4 months; 2 mg E2 + 1.0 mg NETA, 936.3 months. The average number of months of exposure for subjects in each treatment group ranged from 17.9 to 19.4 months. Approximately 50% of the subjects in each treatment group were exposed to treatment for at least 24 months.

EST/PD/4/N+S- The percentage of women who were exposed to E2 for more than 21 menstrual cycles ranged from 85 to 90%, while only 72% of the women in the placebo group were exposed for 21 menstrual cycles or longer. For women who were 100% compliant during the 24 months of the trial, the total exposure to active trial products was as follows: 336 mg E2 for the women in the 0.5 mg E2 group, 672 mg E2 for the women in the 1 mg E3 group, and 1344 mg E2 for those in the 2 mg E2 group.

ALD-1537- The extent of exposure to the two Activelle ———— preparations during the trial was comparable, with a mean exposure of 23.8 \pm 4.1 weeks (range 1.3 to 29.3 weeks) for the

ALD 0.25 treatment group and of 23.6 ± 4.7 weeks (range 0.4 to 30.0 weeks) for the ALD 0.1 group. The extent of exposure in the placebo treatment group was slightly lower, with a mean exposure of 21.4 ± 6.9 weeks (range 0.6 to 31.6 weeks).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None

7.2.2.2 Postmarketing experience

Activella 1mg E2/0.5 mg NETA has been approved in the US since 11/18/1998 for the treatment of moderate to severe vasomotor symptoms associated with menopause and treatment of vulvar or vaginal atrophy and since 4/11/2000 for the prevention of PMO.

7.2.2.3 Literature

See section 8.6.

7.2.3 Adequacy of Overall Clinical Experience

Activella has been adequately assessed in the clinical trials submitted in this application for the prevention of PMO as long as its use continues to be limited to the shortest duration necessary consistent with treatment goals.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special animal and/or in vitro testing had been previously reviewed and found to be acceptable. No new information was submitted in this application.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing had been previously reviewed and found to be acceptable. No new information was submitted in this application.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolic, clearance and interaction information had been previously reviewed and found to be acceptable. No new information was submitted in this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Even though the 6 to 26-month studies submitted in this application showed no definite evidence of higher rates of myocardial infarction, stroke, pulmonary emboli, deep venous thrombosis or invasive breast cancer in postmenopausal women treated with low dose oral conjugated estrogens compared to placebo it is not possible to extend these data to longer durations of therapy. It is recommended that physicians continue to monitor patients for these potential AEs, especially in patients who may require extended therapy beyond the 2-year period assessed in the current clinical trials.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted and reviewed were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

Not applicable.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusion

The incidence and types of treatment related adverse events seen in the trials reviewed in this submission were not unexpected for estrogen replacement therapy. While these 6 to 26-month studies showed no evidence of an increase in cardiovascular events, worsening of potential markers for cardiovascular disease or an increase in the risk for breast cancer with low dose estrogen compared to placebo, it is not possible to compare these data to longer studies like the 5-year WHI. Therefore, with sufficient treatment exposure it is still possible that higher rates of myocardial infarction, stroke, pulmonary emboli, deep venous thrombosis or invasive breast cancer may be seen in postmenopausal women even with low dose oral conjugated estrogens compared to placebo. For this reason, use of this low dose estrogen progestin formulation should continue to be limited to the shortest duration necessary consistent with treatment goals. In addition, women with hypertension, active cardiovascular disease, thromboembolic disorders or suspicious lesions by mammogram were not included in these trials so the risk profile for such patients was not assessed, and use in these subpopulations cannot be recommended.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Study EST/PD/4/N+S was inadequately designed to support the proposed postmenopausal osteoporosis indication, and was not used to support labeling of the new low dose product. Therefore there was no benefit to be gained in pooling the study results.

7.4.2 Explorations for Predictive Factors

The SAS datasets submitted by the sponsor were reanalyzed using JMP 5.1 software to determine if there was any correlation between baseline LS BMD and change in BMD in response to therapy. This analysis was performed specifically to see if the effect of estrogens on BMD decreased at higher baseline BMD values, in which case, the indication for prevention of PMO with Activella could be limited to postmenopausal women with baseline BMDs below a threshold level. The reanalyzed data showed that while the drop in BMD seen in patients in the placebo group was greatest in those patients with the lowest baseline LS BMD that the increase in LS BMD seen with 0.5mg of E2 was evident over the entire range of baseline LS BMD values tested. In the 2mg E2 group there was also a trend suggesting the increase in LS BMD was greater at the higher baseline LS BMD values with this higher dose of estrogen. Therefore, these data would not support that the indication for prevention of PMO be restricted due to baseline LS BMD. These results are consistent with the subgroup analyses performed by the FDA statistician, Dr. Liu, which also showed no significant treatment interaction based on baseline LS BMD ≤ 1 , between 1 and 1.2 and > 1.2 .

Since all study subjects were females between 44 and 55 and $>90\%$ Caucasian, no subgroup analyses were performed to look at the effects of gender, age or race on efficacy outcomes.

7.4.3 Causality Determination

No clear causality determination was observed in the studies in this submission. Breast pain was seen more commonly in the continuous combined treatment groups, and endometrial hyperplasia/post-menopausal bleeding seen primarily in the E2 alone treatment groups suggesting AEs that were possibly causally related.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed regimen is one tablet of Activella 0.5mg E2/0.1mg NETA daily to be given for the shortest duration consistent with treatment goals and risks for the individual woman. This is a

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low dose estrogen version of Activella which was originally approved for the treatment of postmenopausal osteoporosis as Activella 1mg E2/0.5mg NETA in April 2000.

8.2 Drug-Drug Interactions

Study ALD-1640 reviewed by Sandra Suarez in DRUP, confirmed that coadministration of E2 (0.5 to 1mg) and NETA (0.1 to 0.5mg) did not affect the pharmacokinetics of either E2 or NETA, consistent with information which is already present in the currently approved Activella 1mg E2/0.5mg NETA label. No other drug-drug interaction studies were included in this submission.

8.3 Special Populations

No special demographic subgroup analyses were performed in the 2-year BMD studies, KLIM/PD/11/USA and EST/PD/4/N+S.

No geriatric studies were done as the indication is for short term treatment of postmenopausal women.

8.4 Pediatrics

There were no pediatric studies in this submission. The sponsor should be given a pediatric waiver because it is inappropriate to give hormone replacement therapy to pediatric patients to treat osteoporosis.

8.5 Advisory Committee Meeting

There was no need for an advisory committee meeting to evaluate this NDA submission.

8.6 Literature Review

A Medline (1966-2003) database search for randomized controlled trials (keywords: low-dose estrogen, minimum dose AND estrogen, menopause, and osteoporosis) regarding hot flashes, endometrial hyperplasia, vaginal bleeding, breast tenderness, and bone density was performed by Dr. Crandall and published in the Journal of Women's Health². She found the decrease in hot flashes with half-strength estrogens, range 60%-70%, less than the 80%-90% reduction with standard dosing. Some low-dose preparations preserve lumbar and femoral bone density (although the degree of effect and quality of evidence vary among preparations). Bone density effects were dose dependent for conjugated equine estrogen (CEE), transdermal estradiol ethinyl (E2), norethindrone acetate (E2/NETA), oral E2, and esterified estrogens, which is consistent with the result seen in KLIM/PD/11/USA. Bone preservation is likely to be less efficacious with

2 Crandall C., J Womens Health 12(8):723-747, 2003. © 2003, Low-Dose Estrogen Therapy for Menopausal Women: A Review of Efficacy and Safety

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low-dose estrogens than with traditional doses. Low-dose estrogen alone may not protect bone unless adequate calcium is given. Breast tenderness and skeletal effects are likely dose dependent. The longest endometrial safety data are 2-year data, reported for 5 µg/1 mg EE2/NETA and for 0.3 mg/day esterified estrogens. Some low-dose preparations have better vaginal bleeding profiles than do higher dose preparations. Breast tenderness is not totally averted with new lower dose preparations. There are no fracture, breast cancer, or cardiovascular long term outcome data and a general lack of direct head to head comparisons involving low-dose preparations. Dr. Crandall concluded that serious adverse effects linked with traditional doses of estrogens may not be averted with lower dose preparations.

8.7 Postmarketing Risk-Management Plan

The sponsor concluded that a risk minimization action plan (MAP) is not required at the present time based on the following justification:

- No individual risk factors have been identified in the logistic regression analyses performed to date.
- The data from the ALD-1537 trial does not warrant any special measures with regard to risk communication
- The company core data sheet is adequately updated with the potential risks identified to date and with the patient groups not studied to date due to exclusion.
- The lower strength of an already marketed product.

The Office of Surveillance and Epidemiology has reviewed the submitted RMP and agrees that it does not identify a specific safety concern for which a Risk MAP to minimize risk would be normally associated.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

There was a statistically significant increase in lumbar spine, proximal femur and femoral trochanter BMD observed at 2 years in postmenopausal women treated with 0.5mg E2 relative to placebo. Higher BMD values were also observed at 2 years in postmenopausal women treated with E2 and 0.25 or 0.5mg NETA relative to E2 alone. Therefore, it is safe to conclude that the to-be-marketed formulation, Activella 0.5mg E2/0.1mg NETA, would be efficacious in slowing the progression of osteoporosis in postmenopausal women relative to placebo.

The incidence and types of treatment related adverse events seen in the trials reviewed in this submission were not unexpected for estrogen replacement therapy. Breast pain was seen more

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commonly with combined estrogen/progestin formulations whereas endometrial hyperplasia/postmenopausal bleeding were seen primarily in the estrogen alone groups. There was no increase in cardiovascular events, worsening of potential markers for cardiovascular disease or increase in the risk for breast cancer with low dose estrogen compared to placebo in trials of up to 2 years duration. However, it is not possible to rule out that higher rates of myocardial infarction, stroke, pulmonary emboli, deep venous thrombosis or invasive breast cancer may be seen in postmenopausal women with low dose oral conjugated estrogens compared to placebo during longer durations of treatment. For this reason, use of this low dose estrogen progestin formulation should continue to be limited to the shortest duration necessary consistent with treatment goals. In addition, women with hypertension, active cardiovascular disease, thromboembolic disorders or suspicious lesions by mammogram were not included in these trials so the risk profile for such patients was not assessed, and use in these subpopulations cannot be recommended.

9.2 Recommendation on Regulatory Action

Activella 0.5mg E2/0.1 mg NETA should be approved for the prevention of postmenopausal osteoporosis.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activity is recommended as this is a lower strength of an already approved product.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

See line by line review section 10.2.

9.5 Comments to Applicant

1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

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10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 KLIM/PD/11/USA- A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study 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.

STUDY DESIGN

Study KLIM/PD/11/USA was originally submitted 6/10/99 as part of NDA 21-103 and reviewed by Joanna Zawadzki, primary medical reviewer, Japo Choudhury, statistician, and Eric Colman, team leader (final approval 4/11/2000). Study KLIM/PD/11/USA was the pivotal study leading to the approval of Activella (1mg E2/0.5mg NETA) for the prevention and management of PMO. This current review will focus on key points in this study which relate to the current indication for 0.5mg E2/0.1mg NETA Activella and the reader is directed to the original reviews for a more comprehensive analysis of this study.

KLIM/PD/11/USA was a double-blind, randomized, placebo-controlled, parallel-group, 26 month study in healthy postmenopausal women 45 years of age or older with an intact uterus. Women were one to 5 years post menopause and had a BMD score less than two standard deviations below the young adult normal mean (i.e. $>0.827\text{gm/cm}^2$ for L_{1-4} or $>0.940\text{gm/cm}^2$ for L_{1-4}). A total of 737 women were screened, 327 were randomized, and 189 completed the study. Exclusion criteria included but were not limited to: MI in the last 6 months, history of stroke, thrombophlebitis or thromboembolic disorder, heavy cigarette smoker (>20 cigarettes per day), $>30\%$ above ideal body weight, systolic BP $\geq 160\text{mm Hg}$ or diastolic BP $> 100 \geq \text{mm Hg}$, evidence of nontraumatic osteoporotic fracture within the past 2 years, chronic treatment with steroids, endometrial hyperplasia or endometrial thickness $> 6\text{mm}$.

Subjects were randomly assigned to one of seven treatment groups:

1. 2 mg E2 and 1.0 mg NETA
2. 1 mg E2 and 0.5 mg NETA
3. 1 mg E2 and 0.25 mg NETA
4. 1 mg E2 alone
5. 0.5 mg E2 alone
6. 0.25 mg E2 alone
7. Placebo

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All subjects were administered calcium supplementation (1000mg/day) as instructed by the investigator. In general, discontinuation rates were similar for the combination treatment groups (33 to 40%) compared to the placebo group (40%). They were somewhat higher for the estrogen alone groups (44 to 56%), which had a higher frequency of endometrial hyperplasia and bleeding.

Efficacy was assessed using dual energy x-ray absorptiometry to determine bone mineral density (BMD) of the lumbar spine (AP view, L 1-4) and hip (femoral neck and trochanteric region). Percent change from baseline at 13, 19, and 26 months in BMD was determined for the lumbar spine (primary efficacy) and for the hip (secondary efficacy). Bone biochemical markers including bone-specific serum alkaline phosphatase, urinary pyridinoline, and urinary deoxypyridinoline were also measured at baseline, 6, 13, 19, and 26 months (secondary efficacy endpoints). Comparisons were made using ANOVA and ANCOVA analyses.

Special safety assessments included gynecological examinations (breast and pelvic), mammography, endometrial biopsy, Pap smear and vaginal ultrasound.

The populations analyzed were defined as follows:

- Intent to Treat (ITT)- included all randomized women, used for safety analysis
- Modified ITT- included all treated women with baseline data and at least one post-randomization BMD measurement, used for analysis of BMD measurements
- Per-Protocol (PP)- included women who completed at least 24 months of the study, had Visit 10 data, and did not violate the major efficacy related inclusion criteria (1, 2, 3, and 4, see section 4.3.2.1 pg 28 of sponsor's clinical trial report) or exclusion criteria (1, 2, 3, 4, 5, 17, and 18, see section 4.3.2.2 pg 29 of sponsor's clinical trial report), used for analysis of BMD measurements

There were no significant differences in baseline demographic characteristics among the treatment groups. The subjects were primarily white (range 83 to 98%), had a mean age of 53 years (range 52.3 to 53.5 years), averaged 3 years post menopause (range 2.5 to 3.1 years). The treatment groups had similar mean baseline LS BMD of 1.05 to 1.11g/cm² and low mean rates of previous hormone replacement therapy (4.2 to 8.7%).

EFFICACY ANALYSIS

BMD values at the lumbar spine increased with increasing estrogen dosage, while BMD decreased in women in the placebo group. Although, the study was not designed to evaluate differences between active-treatment groups, it did appear to show a dose-related trend in increase in LS BMD with respect to estrogen dosage. The modified ITT, LOCF analysis of the percent change from baseline for BMD of lumbar spine showed that the placebo group had a mean 2.12% decrease in BMD (Table 4 and Figure 1). The 0.5mg E2 treatment group showed a mean increase of 2.26%, in BMD after 2 years, which was statistically significant, $p < 0.001$, 95% confidence intervals of 2.89 to 5.86. The net difference from placebo was $2.26 - (-2.12\%) = 4.38\%$. The Per Protocol analyses at 26 months gave similar results for LS BMD. It showed a mean decrease of 2.04% in the placebo group compared to an increase of 2.21% with 0.5mg of E2, for

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a net difference of 4.25%, p<0.001. BMD values at the lumbar spine increased with increasing NETA dosage at a constant estrogen dose of 1mg e.g. 0mg NETA +2.76%, 0.25mg NETA +3.54%, 0.5mg NETA +3.80% (see Table 4).

Table 4

Study KLIM/PD/11/USA-Primary Efficacy Analysis: LS BMD
(Data taken from sponsor's Table 8.2.1.1 Clinical Trial Report)

TABLE 8.2.1.1. BMD OF LUMBAR SPINE: % CHANGE FROM BASELINE - LOCF

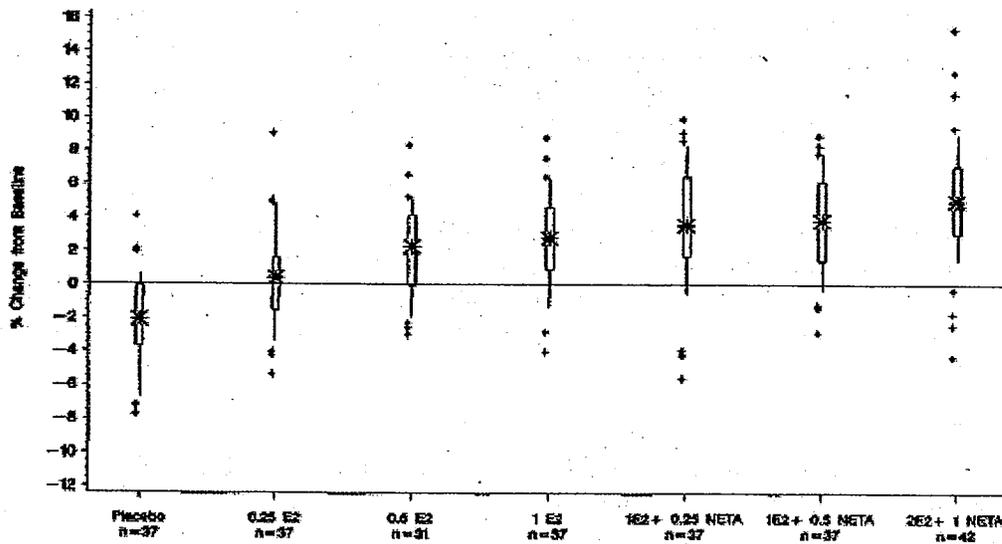
Treatment	N	Mean	SD	Median	Range	P-value	Compared to Placebo	
							Difference	95 % CI
Placebo	37	-2.12	2.860	-2.06	-7.59 - 4.24			
1 mg E ₂ + 0.25 NETA	37	3.54	3.679	3.64	-5.40 - 10.10	<0.001	5.66	(4.18, 7.14)
1 mg E ₂ + 0.5 NETA	37	3.80	3.034	3.78	-2.69 - 9.06	<0.001	5.92	(4.44, 7.40)
0.25 mg E ₂	37	0.39	2.927	0.56	-5.18 - 9.21	0.001	2.51	(1.09, 3.92)
0.5 mg E ₂	31	2.26	2.760	2.44	-2.82 - 8.48	<0.001	4.37	(2.89, 5.86)
1.0 mg E ₂	37	2.76	2.877	2.95	-3.84 - 8.94	<0.001	4.88	(3.46, 6.30)
2.0 mg E ₂ + 1.0 NETA	42	4.99	3.750	4.98	-4.12 - 15.52	<0.001	7.11	(5.74, 8.48)

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

Figure 1

Study KLIM/PD/11/USA-Primary Efficacy Analysis: LS BMD
(Data taken from sponsor's Figure 8.2.1.1A Clinical Trial Report)

FIGURE 8.2.1.1A. BMD OF LUMBAR SPINE: % CHANGE FROM BASELINE - LOCF



* mean

Statistically significant changes from baseline were also seen for the secondary endpoints BMD at the proximal femur.

Table 5						
Study KLIM/PD/11/USA-Secondary Efficacy Analysis: Proximal Femur						
(Data taken from sponsor's Table 8.2.1.2 Clinical Trial Report)						
Treatment site	N	Mean % BMD	SD	P-value	Net difference	95% CI
Femoral neck						
Placebo	37	-2.26	3.4			
0.5mg E2	30	0.26	2.9	<0.007	2.52	(0.070, 4.34)
Femoral trochanter						
Placebo	37	-1.95	4.3			
0.5mg E2	30	1.74	4.1	<0.002	4.48	(2.26, 6.70)

Compared to the highest percentage of subjects who showed an increase in BMD above baseline ($\geq 0\%$ BMD) in the highest combination dose group i.e. 2mg E2 + 1.0 NETA, the effect seen with 0.5mg of E2 was intermediate but still substantially greater than seen in the placebo groups (see Table 6).

Table 6						
Study KLIM/PD/11/USA- Subjects with $\geq 0\%$ BMD from baseline, LOCF						
(Data taken from sponsor's Table 8.2.1.3 Clinical Trial Report)						
Treatment	Lumbar Spine		Femoral Neck		Femoral Trochanter	
	N	%	N	%	N	%
Placebo	37	22	37	27	42	32
0.5mg E2	31	74	30	57	36	67
2mg E2 + 1.0 NETA	42	91	42	76	44	83

These data cannot be used to conclude that some patients may not be responding to E2, because even subjects who had a decrease in BMD at specific sites may have observed an even greater decrease in BMD in the absence of treatment with estrogen.

Urinary bone markers were generally also supportive of the BMD increases seen with estrogen. Urinary pyridinoline, and deoxypyridinoline have been used to estimate bone turnover. The urinary concentrations of pyridinoline, and deoxypyridinoline decreased in the active control groups, consistent with estrogen acting as an anti-resorptive agent. While bone specific alkaline phosphatase increased in all treatment arms compared to baseline, the increase, a measure of bone turnover, was smaller in the active treatment arms, also consistent with estrogen acting as an anti-resorptive agent.

Table 7			
Study KLIM/PD/11/USA, Bone Turnover Marker Data, LOCF			
(Data taken from Table 8.2.2A Clinical Trial Report)			
Bone Marker	Treatment group	Number	Median % Change from Baseline
Bone Specific Alkaline Phosphatase (ng/mL)	Placebo	41	114
	0.5mg E2	36	90
Urinary Pyridinoline (nmol/mmol)	Placebo	40	-6
	0.5mg E2	35	-22
Urinary Deoxypyridinoline (nmol/mmol)	Placebo	40	-9
	0.5mg E2	35	-22

SAFETY RESULTS

Deaths

One subject in the 1mg E2 + 0.5mg NETA group died from a metastatic adenocarcinoma 2 months after withdrawing from the study. She had received 439 days of therapy before the study medication was stopped. A tentative diagnosis of ovarian carcinoma was made but it was not confirmed because an autopsy was not performed. The clinical investigator deemed this adenocarcinoma was unlikely to be due to the study drug.

Serious Adverse Events

There were 18 women with 23 serious adverse events reported in the combined E2 treatment groups (18/279=6.5%) compared to only one in the placebo group (1/48= 2.1%). In the 0.5mg E2 alone treatment group there were 3 women (3/44=6.8%) with 4 serious adverse events (e.g. viral infection, back pain, uterovaginal prolapse, and cholelithiasis), which were all unlikely or at most possibly related to the study drug.

There were two cases of breast cancer deemed by the clinical investigators as possibly or probably related to the study treatment: a malignant breast neoplasm in one patient treated with a higher dose of E2 (i.e. 1.0mg E2 alone for 729 days) and in one patient treated with a lower dose of E2 (i.e. 0.25mg E2 alone for 495 days). In addition to these 2 cases of malignant breast cancer there were 6 other non serious clinically significant mammography results in the E2 or E2 + NETA treatment groups compared to none in the placebo group.

E2 alone

1mgE2 (49 y/o day 720)
 0.25mg E2 (57 y/o day 362)

E2 + NETA

2mgE2+ 1mg NETA (47 y/o day 477)
 1mgE2+0.25mg NETA (56 y/o day 216, 52 y/o day 729)
 1mgE2 + 0.5mg NETA (58y/o day 364)

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While these data suggest that estrogens may contribute to abnormal breast findings including cancer, the number of patients in this study is too small to come to any clear conclusions. Recent findings from the Women's Health Initiative, which has enrolled over 160,000 women over the past 15 years, suggested that unopposed estrogen was not associated with an increased risk of breast cancer but that the progesterone component of combined hormone therapy was important at increasing the risk. In study KLIM/PD/11/USA there were more abnormal findings in patients on combined therapy but the two malignancies were in patients taking estrogen alone. The inconsistency between this study and the WHI results shows how difficult it is to draw credible conclusions from studies with a small number of patients.

In KLIM/PD/11/USA, endometrial disorders were seen in one placebo patient (1/48=2.1%, hyperplasia), one patient with 1mg E2 + 0.25mg NETA (1/49=2.0%, endometriosis), one patient with 1mg E2 alone (1/46=2.2%, hyperplasia), one patient with 0.25mg E2 alone (1/45=2.2%, hyperplasia and endometriosis) and in one patient with 2mg E2 + 1.0mg NETA (1/48=2.1%, endometrial disorder unspecified). Again, the small number of patients in each treatment group makes it difficult to draw any clear conclusions from these data. However, endometrial biopsies confirmed the protective effect of NETA on the endometrium as there were no cases of endometrial hyperplasia with combined continuous treatment with NETA doses of 0.25mg or higher. In the 1mg E2 alone group there were 9 out of 32 (28%) positive biopsies. In the 0.5 mg E2 alone group there was 1 out of 30 (3%) positive biopsies. There were no positive biopsies in the 0.25 mg E2 alone group. There was 1 out of 35 (3%) positive biopsies in the placebo group which was unexpected and for which the sponsor could not provide a clear explanation. The protective effect of NETA on the endometrium was also observed in measurements of the mean or median increase in endometrial thickness between the treatment groups although individual patient data was not provided.

Dropouts and Other Significant Events

Six women had serious adverse events that resulted in withdrawal from the study (see sponsor's data Table 9.2.2, KLIM/PD/11/USA Clinical Study Report).

- placebo group
 - endometrial hyperplasia
- E2 alone groups
 - uterovaginal prolapse
 - malignant breast neoplasm and
 - pituitary neoplasm
- E2 + NETA combination treatment groups
 - endometriosis and
 - metastatic adenocarcinoma

Only the cases of endometrial hyperplasia and breast neoplasm were deemed possibly related to the study drug by the clinical investigator.

Additional nonserious adverse events that lead to the discontinuation of patients in the treatment groups were

- placebo group
 - breast pain
 - endometrial hyperplasia
 - hot flashes
 - depression/emotional lability
- E2 alone groups
 - post menopausal bleeding
 - breast pain
 - endometrial hyperplasia
 - hot flashes
 - abdominal pain
 - weight gain
 - depression/emotional lability
- E2 + NETA combination treatment groups
 - post menopausal bleeding
 - breast pain
 - hot flashes
 - abdominal pain
 - depression/emotional lability
 - back pain/Tarlov's cyst

In summary, the incidence and types of treatment related adverse events were not unexpected for hormone replacement therapy or estrogen replacement therapy.

Common Adverse Events

Treatment emergent AEs reported by > 5% of the women in any group are summarized by system-organ class in Table 9. The incidence of AEs seen with 0.5mg E2 (n=11, 23%) was similar to the placebo group (n=11, 25%). AEs categorized as reproductive disorders were the most commonly reported events with breast pain seen more commonly in the continuous combined treatment groups, and endometrial hyperplasia/post-menopausal bleeding seen primarily in the E2 alone treatment groups. AEs occurring in at least 2 more patients in the 0.5mg E2 group compared to the placebo group were seen in order of occurrence as abdominal pain (5 vs. 0), dizziness, flatulence, back pain and rash (4 vs. 0, 1, 2, 2, respectively), and postmenopausal bleeding (3 vs. 0). These AEs were not unexpected for subjects receiving estrogen replacement therapy.

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Table 9

Study KLIM/PD/11/USA-AEs Occurring at $\geq 5\%$ in Any Treatment Group
(Data taken from Table 9.1.1.A Clinical Trial Report)

TABLE 9.1.1.A. NUMBER (%) OF WOMEN WITH TEAEs OCCURRING AT $\geq 5\%$ IN ANY TREATMENT GROUP

Body system	Placebo (n=48)	1 mg E2 +		E2 Alone		2 mg E2 +	
		0.25 mg NETA (n=49)	0.5 mg NETA (n=47)	0.25 mg (n=45)	0.5 mg (n=44)	1 mg (n=46)	1 mg NETA (n=45)
No. with any TEAE	41 (85.4)	40 (81.6)	39 (83.0)	39 (86.7)	36 (81.8)	40 (87.0)	43 (93.3)
Body as a whole	18 (22.9)	14 (28.6)	16 (34.0)	9 (20.0)	11 (25.0)	10 (21.7)	8 (16.7)
Abdominal pain	0	1 (2.0)	2 (4.3)	4 (8.9)	5 (11.4)	1 (2.2)	2 (4.2)
Back pain	2 (4.2)	4 (8.2)	3 (6.4)	3 (6.7)	4 (9.1)	2 (4.3)	4 (8.3)
Hot flashes	4 (8.3)	0	1 (2.1)	1 (2.2)	1 (2.3)	2 (4.3)	0
Pain	4 (8.3)	4 (8.2)	1 (2.1)	1 (2.2)	1 (2.3)	1 (2.2)	0
CNS and peripheral	4 (8.3)	6 (12.2)	7 (14.9)	8 (17.8)	6 (13.6)	8 (17.4)	6 (12.5)
Dizziness	0	1 (2.0)	2 (4.3)	1 (2.2)	4 (9.1)	1 (2.2)	0
Headache	3 (6.3)	4 (8.2)	5 (10.6)	6 (13.3)	1 (2.3)	5 (10.9)	1 (2.1)
Cardiovascular, general	4 (8.3)	2 (4.1)	2 (4.3)	5 (11.1)	1 (2.3)	0	6 (12.5)
Hypertension	4 (8.3)	1 (2.0)	1 (2.1)	5 (11.1)	0	0	5 (10.4)
Gastro-intestinal	12 (25.0)	14 (28.6)	13 (27.7)	12 (26.7)	7 (15.9)	10 (21.7)	7 (14.6)
Abdominal pain	1 (2.1)	0	1 (2.1)	3 (6.7)	0	3 (6.5)	2 (4.2)
Constipation	3 (6.3)	2 (4.1)	2 (4.3)	1 (2.2)	0	3 (6.5)	0
Diarrhea	1 (2.1)	1 (2.0)	2 (4.3)	1 (2.2)	0	4 (8.7)	1 (2.1)
Dyspepsia	2 (4.2)	2 (4.1)	1 (2.1)	0	1 (2.3)	3 (6.5)	0
Flatulence	1 (2.1)	2 (4.1)	2 (4.3)	1 (2.2)	4 (9.1)	1 (2.2)	0
Gastroenteritis	2 (4.2)	1 (2.0)	3 (6.4)	0	0	0	0
Nausea	0	0	5 (10.6)	1 (2.2)	1 (2.3)	0	0
Tooth disorder	1 (2.1)	3 (6.1)	0	1 (2.2)	0	1 (2.2)	1 (2.1)
Metabolic and nutritional	4 (8.3)	4 (8.2)	6 (12.8)	6 (13.3)	5 (11.4)	3 (6.5)	5 (10.4)
Weight increase	3 (6.3)	2 (4.1)	4 (8.5)	6 (13.3)	3 (6.8)	3 (6.5)	4 (8.3)
Musculo-skeletal	7 (14.6)	3 (6.1)	4 (8.5)	10 (22.2)	8 (18.2)	7 (15.2)	6 (12.5)
Arthralgia	3 (6.3)	2 (4.1)	2 (4.3)	2 (4.4)	4 (9.1)	4 (8.7)	1 (2.1)
Fracture pathological	0	0	0	4 (8.9)	0	0	2 (4.2)
Neoplasms	12 (25.0)	7 (14.3)	7 (14.9)	14 (31.1)	7 (15.9)	16 (34.8)	19 (39.6)
Breast fibroadenosis	0	0	1 (2.1)	0	1 (2.3)	1 (2.2)	3 (6.3)
Cervical smear test positive	2 (4.2)	0	1 (2.1)	3 (6.7)	0	1 (2.2)	2 (4.2)
Cervical uterine polyp	2 (4.2)	0	3 (6.4)	0	0	1 (2.2)	3 (6.3)
Ovarian cyst	4 (8.3)	2 (4.1)	0	5 (11.1)	4 (9.1)	4 (8.7)	2 (4.2)
Uterine fibroid	4 (8.3)	3 (6.1)	2 (4.3)	8 (17.8)	3 (6.8)	10 (21.7)	14 (29.2)
Psychiatric disorders	5 (10.4)	6 (12.2)	6 (12.8)	3 (6.7)	3 (6.8)	8 (17.4)	5 (10.4)
Anxiety	0	1 (2.0)	0	0	0	4 (8.7)	2 (4.2)
Depression	0	4 (8.2)	1 (2.1)	0	0	2 (4.3)	1 (2.1)
Emotional lability	0	0	3 (6.4)	0	0	1 (2.2)	0
Insomnia	4 (8.3)	0	0	1 (2.2)	1 (2.3)	0	1 (2.1)

(table continues)

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Table 9 (continued)

TABLE 9.1.1.A. NUMBER (%) OF WOMEN WITH TEAEs OCCURRING AT ≥ 5% IN ANY TREATMENT GROUP

Body system Event	Placebo (n=48)	1 mg E2 +		E2 Alone			2 mg E2 +
		0.25 mg NETA (n=49)	0.5 mg NETA (n=47)	0.25 mg (n=45)	0.5 mg (n=44)	1 mg (n=46)	1 mg NETA (n=48)
Reproductive disorders	9 (18.8)	15 (30.6)	15 (31.9)	6 (13.3)	15 (34.1)	26 (56.5)	18 (37.5)
Breast disorders	1 (2.1)	1 (2.0)	0	0	1 (2.3)	3 (6.5)	1 (2.1)
Breast pain	4 (8.3)	5 (10.2)	8 (17.0)	1 (2.2)	2 (4.5)	4 (8.7)	4 (8.3)
Endometrial disorder	3 (6.3)	1 (2.0)	0	2 (4.4)	4 (9.1)	12 (26.1)	4 (8.3)
Endometrial hyperplasia	1 (2.1)	0	0	1 (2.2)	1 (2.3)	6 (13.0)	0
Post-menopausal bleeding	0	3 (6.1)	5 (10.6)	1 (2.2)	3 (6.8)	9 (19.4)	6 (12.5)
Resistance mechanism	6 (12.5)	9 (18.4)	6 (12.8)	6 (13.3)	8 (18.2)	6 (13.0)	8 (16.7)
Infection viral	3 (6.3)	4 (8.2)	3 (6.4)	4 (8.9)	3 (6.8)	2 (4.3)	4 (8.3)
Mucositis genital	0	4 (8.2)	3 (6.4)	1 (2.2)	1 (2.3)	1 (2.2)	3 (6.3)
Respiratory system	16 (33.3)	12 (24.5)	17 (36.2)	13 (28.9)	13 (29.5)	13 (28.3)	15 (31.3)
Bronchitis	1 (2.1)	1 (2.0)	0	4 (8.9)	1 (2.3)	0	3 (6.3)
Coughing	2 (4.2)	1 (2.0)	2 (4.3)	0	0	1 (2.2)	3 (6.3)
Sinusitis	5 (10.4)	3 (6.1)	7 (14.9)	5 (11.1)	3 (6.8)	6 (13.0)	2 (4.2)
Upper resp tract infection	9 (18.8)	7 (14.3)	7 (14.9)	6 (13.3)	10 (22.7)	8 (17.4)	10 (20.8)
Secondary terms	6 (12.5)	11 (22.4)	13 (27.7)	8 (17.8)	6 (13.6)	8 (17.4)	11 (22.9)
Bite	0	0	0	1 (2.2)	3 (6.8)	0	0
Cyst nos	1 (2.1)	3 (6.1)	2 (4.3)	2 (4.4)	3 (6.8)	4 (8.7)	3 (6.3)
Injury accidental	2 (4.2)	7 (14.3)	8 (17.0)	2 (4.4)	1 (2.3)	6 (13.0)	4 (8.3)
Other events	2 (4.2)	3 (6.1)	3 (6.4)	4 (8.9)	1 (2.3)	1 (2.2)	3 (6.3)
Skin and appendages	9 (18.8)	6 (12.2)	3 (6.4)	8 (17.8)	5 (11.4)	3 (6.5)	3 (6.3)
Rash	2 (4.2)	1 (2.0)	1 (2.1)	1 (2.2)	4 (9.1)	0	2 (4.2)

Laboratory Findings

No clinically significant changes in mean values for clinical chemistry, hematology and urinalysis were seen throughout the study.

Vital Signs

No clinically significant changes in mean values for vital signs or weight were seen throughout the study.

10.1.2 EST/PD/4/N+S A Double-Blind Study Investigating the Effect of Estradiol 0.5 and 1.0 mg and Estradiol 2mg (Estrofem®) Compared to Placebo on Early Postmenopausal Bone Loss

STUDY DESIGN

EST/PD/4/N+S was a double-blind, randomized, placebo-controlled, parallel-group, 24 month study in healthy postmenopausal women 45 years of age or older. All women were hysterectomised, and perimenopausal (FSH >20 IU/L & ≤40IU/L) or postmenopausal (FSH >40 IU/L). 58 (35%) were oophorectomised, of whom 24 (14%) had a bilateral oophorectomy. The mean age at time of oophorectomy ranged from 42.1 to 48.0 years and the mean time since oophorectomy ranged from 2.0 to 7.5 years (median 2 to 3 years). BMD was not a specific entry criteria, but patients with frank osteoporosis were excluded from the study. Baseline BMD score

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measured by dual energy x-ray absorptiometry (DEXA, lunar ~~equipment~~ equipment) ranged from 0.842 to 1.584gm/cm².

Medical Officer's comment-

The indication for prevention of women with PMO does not include perimenopausal women. The data should be reanalyzed excluding perimenopausal women to confirm efficacy in the postmenopausal population.

A total of 171 women were randomized, 166 were exposed to study drugs (123 in Norway and 43 in Sweden) and 139 completed the study. Exclusion criteria included but were not limited to: untreated cardiac disease, concomitant use of lipid lowering agent, history of stroke, deep venous thrombosis or thromboembolic disorder, diastolic BP > 90mm Hg, chronic treatment with steroids, and known, suspected or past history of carcinoma of the breast.

Subjects were randomly assigned to one of four treatment groups:

1. 0.5 mg E2
2. 1 mg E2
3. 2 mg E2
4. Placebo

Daily calcium and Vitamin D supplementation were not provided even though the study was performed in Sweden and Norway which did not routinely supplement dairy products with Vitamin D. So baseline calcium levels were likely to be lower in this trial than in the general US population.

Discontinuation rates were highest for the placebo group 12/43=28%, but half of these cases were due to hot flashes. If these cases are removed from the analysis the rate of discontinuation in the placebo group was similar to that seen in the 1 and 2mg E2 groups i.e. 6/41=14% and 6/42=14%, respectively. The rate of discontinuation was even lower in the 0.5mg group, 3/40=8%, with 2 patients withdrawing for non compliance and one with mild hypertonia.

Efficacy was assessed using DEXA (lunar ~~equipment~~ equipment) to determine BMD of the lumbar spine (AP view, L 1-4) and hip (femoral neck, Ward's triangle and trochanter region). Percent change from baseline at 12, 18, and 24 months in BMD was determined for the lumbar spine (primary efficacy) and for the hip (secondary efficacy). Bone biochemical markers including bone-specific serum osteocalcin, serum pyridinium crosslaps, urinary pyridinium crosslaps, urinary hydroxyproline to creatinine ratio and urinary calcium were also measured at baseline, 6, 12, 18, and 24 months (secondary efficacy endpoints). Comparisons were made using a normal regression model that included the following baseline variables potentially predictive of response: serum osteocalcin, serum pyridinium crosslaps, urinary pyridinium crosslaps, BMD spine, BMI, time since oophorectomy, baseline FSH (> or ≤ 40IU/L) and study center.

Additional secondary efficacy assessments performed only in the Norwegian part of the trial were lipids and lipoproteins, e.g. total cholesterol, triglycerides, LDL-C, HDL-C, apo A-1, apo B-1, and Lp(a). Additional secondary efficacy assessments performed only in the Swedish part

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of the trial were blood clotting parameters, e.g. Factor VIIa, fibrinogen, TAT complex, antithrombin III activity, tPA, PAI-1, and prothrombin fragment I+2.

Special safety assessments included gynecological examinations (breast and pelvic), and mammography.

The populations analyzed were defined as follows:

- Intent to Treat (ITT)- included all treated women with baseline data and at least one post-randomization visit
- Per-Protocol (PP)- included women who met the inclusion/exclusion criteria, completed the trial and were at least 80% compliant with the study medication

There were no differences in baseline demographic characteristics among the treatment groups with respect to age (mean 49 to 50 years, range 44 to 55 years), time since hysterectomy (mean 3.4 to 4.5 years, SD 3.2 to 4.8 years), and baseline LS BMD (mean 1.10 to 1.20g/cm², range 0.84 to 1.58 g/cm²). There were somewhat fewer subjects status post oophorectomy in the placebo group compared to the E2 treatment groups (e.g. placebo 11 (26%), 0.5mg E2 14 (35%), 1mg E2 16 (39%) and 2mg E2 17 (41%)), but there was no clear difference for patients status post bilateral oophorectomy between the groups (e.g. placebo 6 (14%), 0.5mg E2 5 (13%), 1mg E2 9 (22%) and 2mg E2 4 (10%).

EFFICACY ANALYSIS

BMD values at the lumbar spine increased with increasing estrogen dosage, while BMD decreased in women in the placebo group. Although, the study was not designed to evaluate differences between active-treatment groups, it did appear to show a dose-related trend in increase in LS BMD with respect to estrogen dosage. The ITT, LOCF analysis of the percent change from baseline for BMD of lumbar spine showed that the placebo group had a mean 3.47% decrease in BMD (Table 10 and Figure 3). Whereas the lowest dose of estrogen tested, 0.5mg E2, showed only a mean decrease of 0.17%, in BMD after 2 years, which was statistically significant, $p < 0.0001$, 95% confidence intervals of -1.27 to +0.92. The net difference from placebo was $-3.47 - (-0.17\%) = -3.30\%$. The Per Protocol analyses at 24 months gave similar results for LS BMD. It showed a mean decrease of 3.58% in the placebo group compared to a decrease of 0.24% with 0.5mg of E2, for a net difference of $-3.58 - (-0.24) = -3.34\%$, $p < 0.001$.

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Table 10

Study EST/PD/4/N+S- Primary Efficacy Endpoints, LS BMD
(Data taken from sponsor's Table 8-1 Clinical Trial Report)
Table 8-1 BMD at Lumbar Spine (L₁-L₄) (g/cm²)

	placebo	0.5 mg E2	1.0 mg E2	2.0 mg E2
Subjects Exposed	43	40	41	42
Visit 1 (baseline)				
N	40	38	39	40
Mean (SD)	1.198 (0.171)	1.100 (0.130)	1.157 (0.134)	1.160 (0.139)
Min - Max	0.842 - 1.584	0.858 - 1.470	0.871 - 1.423	0.925 - 1.512
Visit 2 (6 months)				
N	36	39	37	36
Mean (SD)	1.179 (0.181)	1.097 (0.135)	1.157 (0.134)	1.156 (0.143)
Min - Max	0.834 - 1.634	0.848 - 1.490	0.870 - 1.437	0.901 - 1.537
Visit 3 (12 months)				
N	32	35	34	35
Mean (SD)	1.190 (0.164)	1.076 (0.110)	1.157 (0.138)	1.173 (0.146)
Min - Max	0.965 - 1.570	0.858 - 1.304	0.861 - 1.453	0.940 - 1.549
Visit 4 (18 months)				
N	29	35	30	34
Mean (SD)	1.202 (0.172)	1.091 (0.114)	1.155 (0.130)	1.170 (0.153)
Min - Max	0.917 - 1.581	0.890 - 1.310	0.864 - 1.436	0.911 - 1.558
Visit 5 (24 months)				
N	29	34	31	34
Mean (SD)	1.196 (0.177)	1.084 (0.112)	1.150 (0.137)	1.173 (0.149)
Min - Max	0.890 - 1.595	0.887 - 1.315	0.864 - 1.418	0.930 - 1.572
Percentage Change To Last Visit				
N	36	37	36	37
Mean (SD)	-3.472 (4.219)	-0.174 (3.277)	0.845 (3.209)	1.806 (3.209)
Median	-2.472	-0.931	0.980	1.026
95% - CI.	[-4.899 - -2.044]	[-1.266 - 0.919]	[-0.241 - 1.931]	[0.736 - 2.876]

Cross-reference: End-of-text tables 5.1 and 6.1

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Figure 3

Study EST/PD/4/N+S -Primary Efficacy Endpoints, LS BMD
 (Data taken from sponsor's Figures 8-1 and 8-2 Clinical Trial Report)

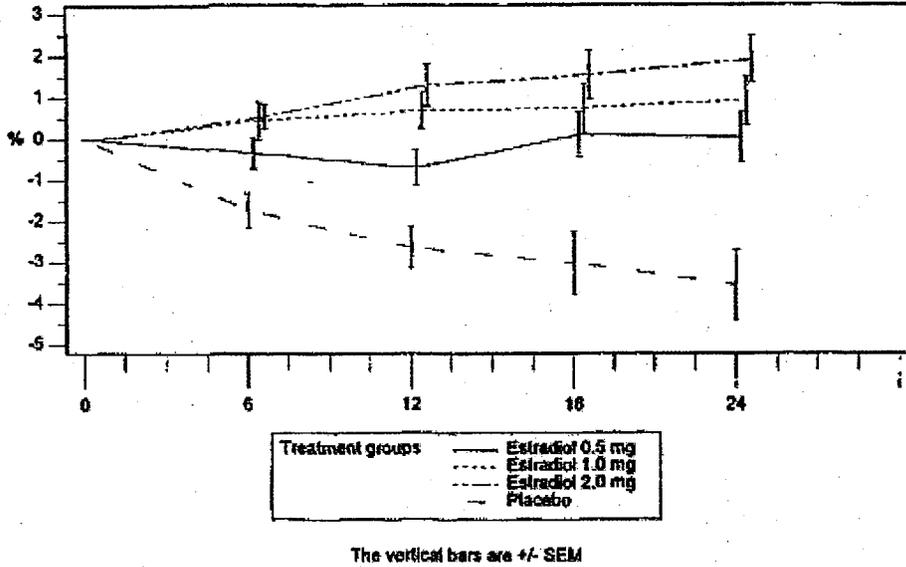
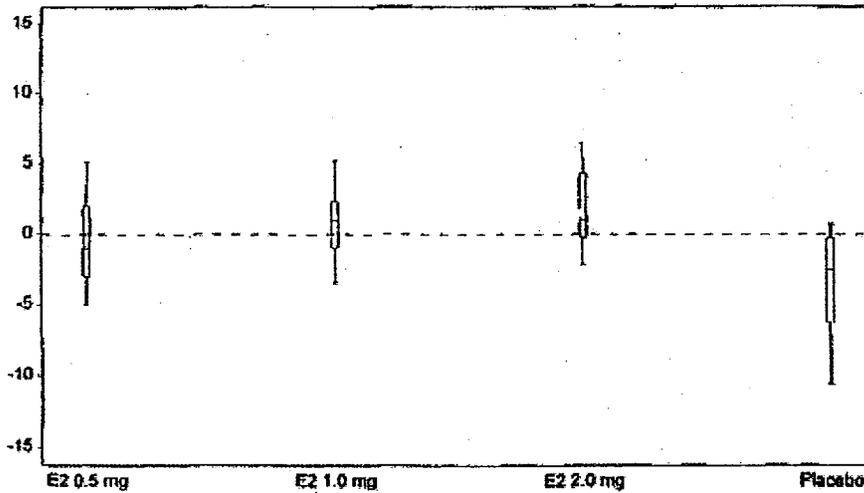


Figure 8-1 Percentage Change in BMD at Lumbar Spine (L₁-L₄)



Boxplots indicate 10%, 25%, 50%, 75%, and 90% fractiles per group

Figure 8-2 Boxplot of Percentage Change in BMD at Lumbar Spine (L₁-L₄)

The SAS datasets submitted by the sponsor were reanalyzed using JMP software to determine if the efficacy was still statistically significant if the perimenopausal subjects with FSH \leq 40IU/L were excluded. LOCF data in the ITT population showed an even greater difference between the placebo group and the Estrogen treatment groups (see Table 11).

Table 11								
Study EST/PD/4/N+S Primary Efficacy Endpoint LS BMD, LOCF Data for all Subjects^a (FSH>20) Compared to Postmenopausal Women^b (FSH>40)								
	N		Median		Mean		95% CIs	
	FSH>20 ^a	FSH>40 ^b						
Placebo	36	22	-2.47	-4.54	-3.47	-4.63	-4.90, -2.04	-6.59, -2.67
0.5mg E2	37	31	-0.93	-0.93	-0.17	-0.04	-1.27, +0.92	-1.23, +1.16
1mg E2	36	22	+0.98	+0.89	+0.85	+1.09	-0.24, +1.93	-0.50, +2.68
2mg E2	37	26	+1.03	+2.19	+1.81	+2.46	+0.74, +2.88	+1.12, +3.80

^aFor sponsor's analysis see Table 10 above. ^bJMP analysis of SAS data sets.

Statistically significant changes from baseline were also seen for the secondary BMD endpoints at the proximal femur and Wards triangle but not at the femoral trochanter (see Table 12).

Table 12						
Study EST/PD/4/N+S Secondary Efficacy Endpoints, Proximal Femur (Data taken from sponsor's Tables 8-3, 8-5 and 8-7 Clinical Trial Report)						
Treatment site	N	Mean % BMD	SD	95% CI	P-value	Net difference in Means
Femoral neck						
Placebo	43	-1.96	3.9	(-3.28, -0.65)		
0.5mg E2	40	+1.76	4.2	(+0.33, +3.19)	<0.001	3.72
Femoral trochanter						
Placebo	37	-0.34	5.5	(-2.19, 1.51)		
0.5mg E2	36	+0.97	5.7	(-0.96, 2.91)	>0.05	1.31
Wards Triangle						
Placebo	43	-2.17	6.5	(-4.33, -0.02)		
0.5mg E2	40	0.74	6.0	(-1.29, +2.77)	<0.05	2.91

The % of patients with an increase in BMD at the lumbar spine, femoral neck and proximal femur (e.g. \geq 0% BMD) in the 0.5mg E2 treatment group, was substantially greater than seen in the placebo group, although less than seen in the 1mg E2 dose group, the dose in Activella 1mg/0.5mg currently approved, (see Table 13).

Table 13						
Study EST/PD/4/N+S Subjects with $\geq 0\%$ BMD from baseline, LOCF						
(Data taken from Table 8-2, 8-4 and 8-6 Clinical Trial Report)						
Treatment	Lumbar Spine		Femoral Neck		Femoral Trochanter	
	N	%	N	%	N	%
Placebo	36	19	37	27	37	38
0.5mg E2	37	41	36	69	36	56
1mg E2	36	61	36	69	36	78

These data cannot be used to conclude that some patients may not be responding to E2, because even subjects who had a decrease in BMD at specific sites may have observed an even greater decrease in BMD in the absence of treatment with estrogen.

Bone markers were generally also supportive of the BMD increases seen with estrogen. Serum osteocalcin, serum pyridinium crosslaps, and urinary pyridinium crosslaps have been used to estimate bone turnover. The serum concentration of osteocalcin and pyridinium crosslaps and the urinary concentrations of pyridinium crosslaps all decreased in the estrogen treatment groups compared to the placebo levels which increased, consistent with estrogen acting as an anti-resorptive agent (see Table 14).

Table 14			
Study EST/PD/4/N+S Bone Turnover Markers, LOCF			
(Data taken from sponsor's Tables 8-9, 8-10 and 8-11 Clinical Studies Report)			
Bone Marker	Treatment group	Number	Mean % Change from Baseline
Serum osteocalcin (ng/mL)	Placebo	43	+8.8
	0.5mg E2	40	-22.2
Serum Pyridinium Crosslaps (pmol/L)	Placebo	43	+16.5
	0.5mg E2	40	-31.0
Urinary Serum Pyridinium Crosslaps (mcg/mmol)	Placebo	43	+27.3
	0.5mg E2	40	-37.5

The SAS datasets submitted by the sponsor were reanalyzed using JMP 5.1 software to determine if there was any correlation between baseline LS BMD and change in BMD in response to therapy. This analysis was performed specifically to see if the effect of estrogens on BMD decreased at higher baseline BMD values, in which case, the indication for prevention of PMO with Activella could be limited to postmenopausal women with baseline BMDs below a threshold level. The reanalyzed data showed that while the drop in BMD seen in patients in the placebo group was greatest in those patients with the lowest baseline LS BMD that the increase in LS BMD seen with 0.5mg of E2 was evident over the entire range of baseline LS BMD values tested. In the 2mg E2 group there was also a trend suggesting the increase in LS BMD was greater at the higher baseline LS BMD values with this higher dose of estrogen. Therefore, these

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data would not support that the indication for prevention of PMO be restricted due to baseline LS BMD. These results are consistent with the subgroup analyses performed by the FDA statistician, Dr. Liu, which also showed no significant treatment interaction based on baseline LS BMD ≤ 1 , between 1 and 1.2 and > 1.2 .

Additional Secondary Efficacy Assessments Lipids/Lipoproteins and Blood Clotting Parameters

With respect to total cholesterol, triglycerides, apolipoprotein B, and lipoprotein(a), there were no significant differences among groups in the changes during treatment. The changes in LDL-cholesterol, HDL-cholesterol, and apolipoprotein A-1 after 24 months of treatment were significantly different between the 2 mg E2 and placebo groups, but no significant changes versus placebo were observed for the 0.5 and 1 mg E2 doses. The lipid changes seen in the high dose estrogen group, i.e. decrease in LDL-C and increase in HDL-C and apolipoprotein A-1, would be considered to be antiatherogenic/protective and would not explain the increase in MIs, stroke and thromboembolic events seen in the WHI Study.

No significant differences were observed among groups after 24 months of treatment with respect to changes in factor VIIIa, fibrinogen, antithrombin III activity, TAT complex, tPA, PAI-1, or prothrombin fragment 1+2.

SAFETY RESULTS

Deaths

One subject in the 1mg E2 group died with ovarian carcinoma. She had a family history of two sisters with ovarian cancer. It is likely that this was unrelated to the study medication.

Serious Adverse Events

There were 17 women with 21 serious adverse events reported in the study, with an equal distribution across treatment groups (e.g. placebo 4/43=9%, 0.5mg E2 4/40=10%, 1mg E2 4/41=10% and 2mg E2 5/42=12%). In the 0.5mg E2 alone treatment group there were four serious adverse events (e.g. accidental injury, gastroenteritis, hyperparathyroidism and varicose vein), which were all unlikely to be related to the study drug.

No cases of abnormal breast findings were reported in the E2 treatment groups. There was one case of breast fibroadenosis which was reported in the placebo group which led to withdrawal of the patient from the study.

Dropouts and Other Significant Events

Twenty women had adverse events that resulted in withdrawal from the study (see sponsor's data Table 9-4, Clinical Study Report).

- placebo group 10/43=23%
 - hot flushes (6)
 - weight increase
 - cystocele

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- diverticulitis
- breast fibroadenosis
- 0.5mg E2 1/40=3%
 - hypertonia
- 1mg E2 5/41=12%
 - Ovarian cancer
 - Weight increase
 - Infection in umbilical region
 - Reduced libido
 - Leucorrhoea
- 2mg E2 4/42=10%
 - Facial edema
 - Weight increase
 - Vaginitis
 - Fatigue

Only the cases of hot flushes, weight increase, facial swelling, leucorrhoea, vaginitis and reduced libido were considered possibly or probably related to the study drug by the clinical investigator.

In summary, the incidence and types of treatment related adverse events were not unexpected for estrogen replacement therapy.

Common Adverse Events

Adverse events reported by $\geq 5\%$ of the women in any treatment group are presented in sponsor's Table 15. The incidence of AEs seen with 0.5mg E2 (n=30, 75%) was slightly lower than seen in the placebo group (n=36, 84%). AEs that were the more common in the placebo group were hot flashes (33% vs. 5 to 7%), sinusitis (12% vs. 0 to 5%) and ovarian cyst (7% vs. 0%), whereas only back pain was more common in all the estrogen treatment groups compared to placebo (5% to 12% vs. 0%). These AEs were not unexpected for subjects receiving estrogen replacement therapy.

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Table 15

Study EST/PD/4/N+S AEs occurring at ≥5% in Any Treatment Group
(Data taken from sponsor's Table 9-1 Clinical Trial Report)

Table 9-1 Adverse Events Reported by ≥5% of Women in a Treatment Group

System Organ Class (SOC)	Placebo		0.3 mg E2		1.0 mg E2		2.0 mg E2	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Subjects Exposed	43		40		41		42	
All Adverse Events	36 (84%)	100	30 (75%)	83	35 (85%)	86	34 (81%)	86
HOT FLASHES	14 (33%)	15	2 (5%)	2	3 (7%)	3	2 (5%)	2
INFLUENZA-LIKE SYMPTOMS	5 (12%)	6	4 (10%)	5	1 (2%)	1	5 (12%)	5
HEADACHE	3 (7%)	3	5 (13%)	6	5 (12%)	5	2 (5%)	2
MYALGIA	3 (7%)	3	1 (3%)	1	3 (7%)	3	3 (7%)	3
BREAST PAIN FEMALE	3 (7%)	1	1 (3%)	1	2 (5%)	2	4 (10%)	4
BACK PAIN (a)	0	0	2 (5%)	2	3 (7%)	3	5 (12%)	5
SINUSITIS	5 (12%)	5	2 (5%)	2	0	0	2 (5%)	2
WEIGHT INCREASE	2 (5%)	2	0	0	4 (10%)	4	1 (2%)	1
BACK PAIN (b)	0	0	3 (8%)	3	3 (7%)	3	1 (2%)	1
RHINITIS	3 (7%)	1	0	0	2 (5%)	2	1 (2%)	1
PNEUMONIA	2 (5%)	2	2 (5%)	2	1 (2%)	1	1 (2%)	1
PAIN	1 (2%)	1	2 (5%)	2	1 (2%)	1	2 (5%)	2
DEPRESSION	1 (2%)	1	0	0	4 (10%)	4	1 (2%)	1
UTEROVAGINAL PROLAPSE	3 (7%)	3	1 (3%)	1	1 (2%)	1	0	0
CYSTITIS	3 (7%)	4	0	0	2 (5%)	3	0	0
PHARYNGITIS	1 (2%)	1	4 (10%)	4	0	0	0	0
RECTAL DISORDER	0	0	1 (3%)	1	2 (5%)	2	2 (5%)	2
DYSPEPSIA	2 (5%)	2	2 (5%)	2	0	0	0	0
ARTHRALGIA	2 (5%)	2	1 (3%)	1	1 (2%)	1	0	0
INJURY ACCIDENTAL	2 (5%)	2	1 (3%)	1	0	0	1 (2%)	1
INFECTION	1 (2%)	1	1 (3%)	1	2 (5%)	2	0	0
BRONCHITIS	1 (2%)	1	0	0	2 (5%)	2	1 (2%)	1
UPPER RESPIRATORY INFECTION	1 (2%)	1	2 (5%)	2	0	0	1 (2%)	1
YERGINITIS	1 (2%)	1	2 (5%)	2	1 (2%)	1	0	0
LYMPHADENOPATHY	0	0	2 (5%)	2	0	0	2 (5%)	2
EDEMA	0	0	1 (3%)	1	1 (2%)	1	2 (5%)	2
OVARIAN CYST	3 (7%)	3	0	0	0	0	0	0
ABDOMINAL PAIN	0	0	0	0	3 (7%)	3	0	0
VEIN VARICOSE	0	0	2 (5%)	2	1 (2%)	1	0	0
GASTROENTERITIS	0	0	2 (5%)	2	0	0	1 (2%)	1
VERTIGO	0	0	0	0	1 (2%)	1	2 (5%)	2
ARTHRITIS	0	0	0	0	1 (2%)	1	2 (5%)	2
VAGINITIS	0	0	0	0	0	0	3 (7%)	4
THYROID ADENOMA	0	0	2 (5%)	2	0	0	0	0

N=Number of subjects
 %=Proportion of exposed subjects having the event
 E=Number of adverse events
 (a) Back pain is included in different system organ classes
 Cross-reference: End-of-text Table 13.1

Laboratory Findings

No clinically significant changes in mean values for clinical chemistry, hematology and urinalysis were seen throughout the study.

Vital Signs

No clinically significant changes in mean values for vital signs or weight were seen throughout the study.

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10.1.3 ALD-1640 Single Dose, Three-way, Cross-Over, Relative Bioavailability Study of Three Oral Formulations for Hormone Replacement Therapy in Postmenopausal Women: 0.5 mg Estradiol + 0.1 mg Norethisterone Acetate, 0.5 mg Estradiol + 0.25 mg Norethisterone Acetate, and 1.0 mg Estradiol + 0.5 mg Norethisterone Acetate

This phase 1 study was formally reviewed in DRUP, HFD-580. The reader is referred to Dr. Sandra Suarez's review for a detailed assessment of these data. A brief synopsis of this study and the key highlights as they refer to the efficacy and safety of 0.5 mg estradiol + 0.1 mg norethisterone acetate for the prevention of PMO is presented here as a reference.

The primary objective of this study was to determine the extent of bioavailability of the two Activelle ——— preparations

0.5 mg estradiol + 0.1 mg norethisterone acetate [Treatment A, two tablets],

0.5 mg estradiol + 0.25 mg norethisterone acetate [Treatment B, two tablets] and

Activelle®

1.0 mg estradiol + 0.5 mg norethisterone acetate [Treatment C, one tablet]

as represented by the area under the concentration-time curves ($AUC_{0-\infty}$) and the rate and extent of absorption as represented by the maximal concentration (C_{max}).

STUDY DESIGN

The trial was an open-label, randomized, single-dose, single-centre, three-way cross-over trial with three single doses of E2/NETA (two tablets of each test preparation of ALD or one tablet of the reference product Activelle®) administered orally under fasting conditions to postmenopausal women in a randomized order. The three in-house periods were separated by a three-week wash-out period. Blood sampling took place over a period of 72 hours after single dosing in order to determine the concentration-time profiles of estradiol, estrone (E2/E1, 18 samples) and estrone sulfate (E1S, 17 samples) in plasma.

Twenty four healthy, postmenopausal, non-smoking or smoking no more than 5 cigarettes per day, Caucasian women, age 50 through 70 years were enrolled and all of them completed the study.

PHARMACOKINETIC RESULTS

Relative bioavailability of estradiol, estrone and NETA were found to be comparable between all three treatments, as all confidence intervals for the pre-specified concentration dependent endpoints of the pharmacokinetic analysis were within the commonly used acceptance range for bioequivalence (0.8 to 1.25).

Table 3

Study ALD-1640 Pharmacokinetic Analysis

Substance Parameter - Method	Ratio A / C with 90% Confidence Interval	Ratio B / C with 90% Confidence Interval
Estradiol (E2) baseline corrected		
AUC(0-t) - Mixed (ln)	95.75% (89.39%, 102.56%)	98.01% (91.49%, 104.97%)
C _{max} - Mixed (ln)	101.18% (90.12%, 113.59%)	95.59% (85.14%, 107.31%)
Estrone (E1) baseline corrected		
AUC(0-t) - Mixed (ln)	97.70% (90.14%, 105.87%)	100.06% (92.32%, 108.43%)
C _{max} - Mixed (ln)	98.34% (90.80%, 106.49%)	99.50% (91.88%, 107.75%)
Norethindrone (NET)		
AUC(0-∞) - Mixed (ln)	102.60% (94.68%, 111.17%) ^a	96.70% (89.39%, 104.59%)
C _{max} - Mixed (ln)	113.12% (106.23%, 120.45%) ^a	98.30% (92.31%, 104.67%)

^a concentration dependant endpoints corrected for dose

The pharmacokinetics of estradiol and estrone were not influenced by the dose of norethisterone acetate within the dose range administered in this study, i.e. 0.2 to 0.5mg, and there is dose adjusted proportional pharmacokinetics of NET within the dose range administered in this study.

10.1.4 ALD-1537-A Six Month Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multicenter Trial to Investigate the Efficacy and Safety of Two Ultra-Low Dose Combinations with 0.5mg Estradiol and 0.1mg or 0.25mg Norethisterone Acetate (Activelle Low Dose 0.1/Activelle Low Dose 0.25) for Treatment of Menopausal Symptoms.

This Phase 3a study was formally reviewed by Dr. Phill Price, medical officer, in DRUP, HFD-580. The reader is referred to Dr. Price's review for a detailed assessment of these data. A brief synopsis of this study and the key highlights as they refer to the safety of the use of 0.5 mg estradiol + 0.1 mg norethisterone acetate for the prevention of PMO is presented here as a reference. The efficacy assessment in this 6 month trial was limited to the improvement of menopausal symptoms and not prevention of PMO and therefore will only be covered briefly in this summary. The safety assessment will focus on the potential long term adverse reactions identified in the WHI report, i.e. cardiovascular events and breast cancer, which are a concern with higher estrogen doses and long term treatment, and will also address the issue whether the low dose of progesterone in this product is sufficient to prevent estrogen induced endometrial hyperplasia in women with an intact uterus.

The primary objective of this study was to assess the change per week in the mean number of moderate to severe hot flashes in post-menopausal women aged 45 to 65 years, who had a minimum of 7 moderate to severe hot flashes per day or 50 moderate to severe hot flashes per week during the 2-week run in period.

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STUDY DESIGN

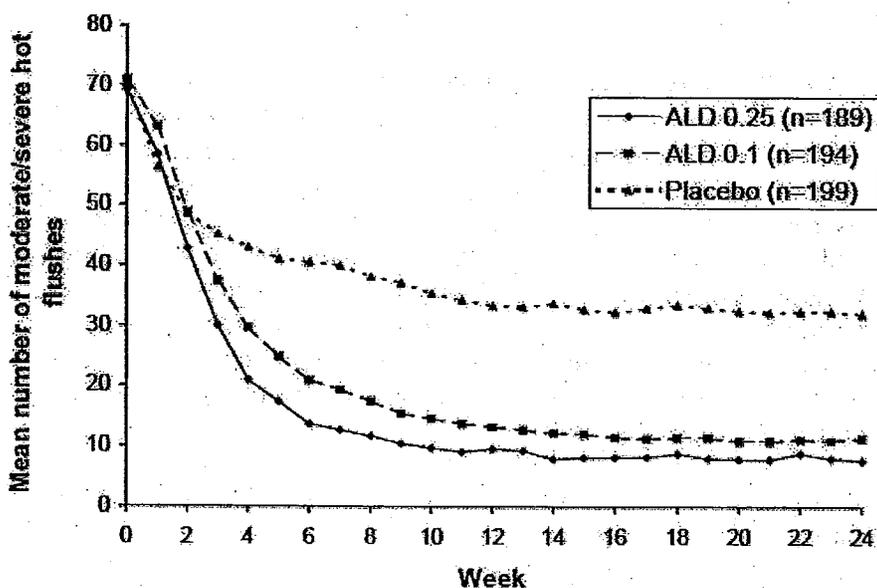
The trial was a double-blind, randomized, multi-centre, multi-national, placebo-controlled, parallel-group trial to show the efficacy and safety of daily treatment with Activelle 0.1 (ALD 0.1) and Activelle 0.25 (ALD 0.25) compared with placebo. The trial comprised a 2-3 week screening period, to assess baseline menopausal symptoms, followed by 24 weeks of treatment with ALD 0.1, ALD 0.25 or placebo.

EFFICACY ANALYSIS

A total of 793 subjects were screened of which 577 were randomized to receive trial medication (194 received ALD 0.1, 182 received ALD 0.25 and 201 received placebo). Both ALD 0.25 and ALD 0.1 resulted in a reduction in the number of moderate to severe hot flashes from week 3 until the end of the study. By week 8 of the trial (the primary time point) the mean number of moderate to severe hot flashes had fallen from 69.2 at baseline to 11.7 in the ALD 0.25 group, from 70.9 at baseline to 17.4 in the ALD 0.1 group and from 70.0 at baseline to 38.2 in the placebo group. Statistically significant treatment differences were seen when comparing ALD 0.25 with placebo and ALD 0.1 with placebo from week 3 to week 24 ($p < 0.001$).

Figure 4

Study ALD-1537 Primary Efficacy Endpoint
Mean Number of Moderate to Severe Hot Flashes (ITT Population)
(Data taken from sponsor's Figure 9-1 Clinical Trial Report)



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SAFETY ANALYSIS

While studies KLIM/PD/11/USA and EST/PD/4/N+S provide 24 and 26 month duration safety data for use of estradiol 0.5mg alone or at higher doses of estradiol, 1 to 2mg, in combination with NETA, study ALD 1537 provides the only safety data on the to-be-marketed formulation, 0.5mg estradiol + 0.1mg NETA.

Deaths

There was only one death reported during the trial, a woman who experienced a fatal myocardial infarction in the placebo group.

Serious Adverse Events

A total of 15 subjects experienced SAEs: 6 in the ALD 0.25 group, 5 in the ALD 0.1 group and 4 in the placebo group.

ALD 0.25

- breast cancer
- pancreatic carcinoma
- pelvic pain
- salpingitis
- myalgia
- mechanical complication of implant

ALD 0.1

- intervertebral disc disorder
- depression and concussion
- dizziness
- ankle fracture
- benign breast neoplasm

Placebo

- fatal myocardial infarction
- muscle rupture
- cholelithiasis
- transient ischemic attack

Only the case of breast cancer in the ALD 0.25 group was considered by the sponsor to be possibly related to the study medication and this will be discussed in more detail under Breast Adverse Events.

Dropouts and Other Significant Events

The incidence of withdrawal was higher in the placebo group (20%) than both the ALD 0.1 (9%) and ALD 0.25 (6%) treatment groups. The major reason for the difference in withdrawal rate was the higher incidence of ineffective therapy in the placebo group (8%) compared with the ALD 0.1 (2%) and ALD 0.25 (1%) groups.

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A total of 31 patients withdrew from the study because of adverse events, 4 subjects (2%) in the ALD 0.25 group and 11 subjects (6%) in the ALD 0.1 group, and 16 subjects (8%) in the placebo group.

ALD 0.25

nervousness
alopecia
back pain, upper abdominal pain, vaginal hemorrhage and pain in extremity
paresthesias

ALD 0.1

hypertension.
intervertebral disc disorder
concussion and depression
groin pain, pain in extremity, hand and leg stiffness
fluid retention, urinary retention, and malaise
pain in extremity
abdominal pain, nausea, diarrhea, dyspepsia, and abnormal LFT
benign breast neoplasm
vaginal hemorrhage and endometrial thickening
headache, dizziness, disturbance in attention
mental impairment

Placebo

gastric disorder
endometrial thickening
hypertension
hypertension, depressed mood, and arthralgia
shoulder pain and muscle rupture
hot flashes
abdominal pain, constipation and dyspepsia
palpitations
abdominal pain, cholelithiasis
vaginal hemorrhage
tinnitus
transient ischemic attack
weight increase
nausea and abdominal pain
migraine
migraine

These adverse event leading to study withdrawal are not unexpected in postmenopausal women on hormone replacement therapy.

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Cardiovascular Adverse Events

The WHI study reported higher rates of myocardial infarction, stroke, pulmonary emboli and deep venous thrombosis in postmenopausal women during 5 years of treatment with oral conjugated estrogens compared to placebo. However, there was no evidence for such an increase in cardiovascular events in this 6 month study with lower dosages of estrogens.

Cardiovascular events occurred in 2% of subjects treated with ALD 0.25, 4% of subjects treated with ALD 0.1, and 6% of subjects in the placebo group. One patient died of a myocardial infarction in the placebo group. There was one adverse report of hypertension in the ALD 0.1 group compared to two reports of hypertension in the placebo group. There was one report of a transient ischemic attack in the placebo group. Both Activelle ——— combinations showed neutral to favorable changes in lipid and lipoprotein, blood clotting parameters and glucose metabolism over the observation period. No mean changes in weight or blood pressure were reported during the 24-week trial period in the Activelle ——— treatment groups. While this 6 month study showed no evidence of an increase in cardiovascular events or worsening of potential markers for cardiovascular disease compared to placebo with this low dose estrogen formulation, it is not possible to extend these data to longer durations of therapy.

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Table 16

Study ALD-1537 Summary of Lipid Parameters
(Data taken from sponsor's Table 10-13 Clinical Trial Report)

Table 10-13 Summary of Lipid Parameters (Safety Population)

Parameter			Week 0	Week 12	Week 24
Total Cholesterol (mmol/L)	ALD 0.25	Number	52	52	52
		Mean ± SD	6.08 ± 1.01	5.74 ± 0.89	5.83 ± 1.00
		Median	5.88	5.62	5.66
		Range	3.94 – 8.13	3.86 – 7.82	3.96 – 8.60
	ALD 0.1	Number	51	48	50
		Mean ± SD	6.12 ± 0.88	5.95 ± 0.83	6.01 ± 0.92
		Median	6.16	5.81	5.95
	Placebo	Range	4.17 – 7.93	4.61 – 8.70	4.01 – 8.26
		Number	55	46	51
		Mean ± SD	6.31 ± 1.02	6.27 ± 0.98	6.32 ± 1.06
		Median	6.19	6.08	6.24
		Range	3.83 – 8.57	4.33 – 9.32	4.48 – 9.53
LDL-Cholesterol (mmol/L)	ALD 0.25	Number	52	52	52
		Mean ± SD	4.03 ± 0.88	3.67 ± 0.76	3.70 ± 0.84
		Median	3.98	3.51	3.60
		Range	2.28 – 6.16	2.18 – 5.21	2.18 – 5.59
	ALD 0.1	Number	51	48	50
		Mean ± SD	4.10 ± 0.79	3.76 ± 0.72	3.81 ± 0.81
		Median	4.14	3.80	3.64
	Placebo	Range	2.43 – 5.70	2.46 – 5.80	1.94 – 5.70
		Number	55	46	51
		Mean ± SD	4.15 ± 0.82	4.00 ± 0.88	4.02 ± 0.86
		Median	4.17	3.73	3.83
		Range	2.46 – 6.03	2.51 – 6.84	2.49 – 6.29
HDL-Cholesterol (mmol/L)	ALD 0.25	Number	52	52	52
		Mean ± SD	2.00 ± 0.31	1.86 ± 0.32	1.85 ± 0.32
		Median	2.01	1.81	1.82
		Range	1.37 – 2.90	1.35 – 2.59	1.27 – 2.75
	ALD 0.1	Number	51	48	50
		Mean ± SD	1.96 ± 0.46	1.96 ± 0.49	1.88 ± 0.45
		Median	1.86	1.86	1.79
	Placebo	Range	1.22 – 3.60	1.04 – 3.76	1.14 – 3.19
		Number	55	46	51
		Mean ± SD	2.06 ± 0.42	2.00 ± 0.40	1.95 ± 0.41
		Median	2.02	2.01	1.92
		Range	1.35 – 3.16	1.14 – 2.98	1.24 – 2.87

Cross-reference EOT Tables 68, 70 and 74

Table 17

Study ALD-1537 Summary of Changes in Lipid Parameters
 (Data taken from sponsor's Table 10-14 Clinical Trial Report)

Table 10-14 Analysis of Changes in Lipid Parameters (Safety Popu

Parameter	Week	ALD 0.25 minus placebo		ALD 0.1 minus placebo	
		Treatment difference ^a	Confidence levels	Treatment difference ^a	Confidence levels
Total Cholesterol (mmol/L)	12	-0.35*	-0.54, -0.18	-0.13	-0.34, 0.02
	24	-0.29*	-0.53, -0.14	-0.15	-0.35, 0.05
LDL-Cholesterol (mmol/L)	12	-0.23	-0.38, -0.07	-0.15	-0.30, 0.01
	24	-0.21*	-0.36, -0.07	-0.17	-0.31, -
HDL-Cholesterol (mmol/L)	12	-0.09*	-0.16, -0.02	0.03	-0.03, 0.10
	24	-0.06	-0.13, 0.01	-0.01	-0.08, 0.06

*Statistically significant ($p \leq 0.044$). ^aBy analysis of covariance.

Table 18

Study ALD-1537 Summary of Hemoglobin A1C
 (Data taken from sponsor's Table 10-15 Clinical Trial Report)

Table 10-15 Summary of HbA_{1c} Levels (%) (Safety Population)

Group		Week 0	Week 12	Week 24
ALD 0.25	Number	52	52	52
	Mean ± SD	5.63 ± 0.44	5.74 ± 0.39	5.64 ± 0.40
	Median	5.70	5.75	5.60
	Range	4.30 – 6.40	4.60 – 6.50	4.30 – 6.40
ALD 0.1	Number	51	48	50
	Mean ± SD	5.59 ± 0.40	5.74 ± 0.36	5.66 ± 0.40
	Median	5.60	5.80	5.70
	Range	4.80 – 6.80	5.00 – 6.70	4.70 – 6.80
Placebo	Number	55	46	49
	Mean ± SD	5.65 ± 0.37	5.93 ± 0.33	5.80 ± 0.30
	Median	5.70	5.90	5.80
	Range	4.60 – 6.50	5.20 – 6.90	5.00 – 6.30

Cross-reference EOT Table 78

Table 19

Study ALD-1537 Summary of Changes in Hemoglobin A1C
 (Data taken from sponsor's Table 10-16 Clinical Trial Report)

Table 10-16 Analysis of Changes in HbA_{1c} (%) (Safety Populati

Week	ALD 0.25 minus placebo		ALD 0.1 minus placebo	
	Treatment difference ^a	Confidence levels	Treatment difference ^a	Confidence levels
12	-0.14*	-0.23, -0.05	-0.11*	-0.21, -0.02
24	-0.16*	-0.24, -0.08	-0.11*	-0.19, -0.03

*Statistically significant (p ≤ 0.037). ^aBy analysis of covariance.

Table 20

Study ALD-1537 Summary of Fibrinogen and Factor VII Levels
 (Data taken from sponsor's Table 10-17 Clinical Trial Report)

Table 10-17 Summary of Fibrinogen and Factor VII Levels (Safety Population)

Parameter		Week 0	Week 12	Week 24	
Fibrinogen (g/L)	ALD 0.25	Number	51	52	52
		Mean ± SD	3.4 ± 0.8	3.2 ± 0.8	3.3 ± 0.7
		Median	3.5	3.0	3.3
		Range	2.2 - 5.9	2.2 - 5.0	2.2 - 5.2
	ALD 0.1	Number	49	48	49
		Mean ± SD	3.0 ± 0.6	2.8 ± 0.6	3.1 ± 0.7
		Median	2.9	2.7	3.0
		Range	1.8 - 5.0	1.5 - 5.5	2.1 - 5.6
	Placebo	Number	54	47	49
		Mean ± SD	3.2 ± 0.7	3.3 ± 0.8	3.4 ± 0.8
		Median	3.1	3.1	3.3
		Range	2.3 - 6.0	2.0 - 5.2	1.6 - 5.2
Factor VII (%)	ALD 0.25	Number	51	52	52
		Mean ± SD	127.7 ± 21.9	121.0 ± 22.5	124.6 ± 19.6
		Median	130.0	125.5	127.5
		Range	78.0 - 183.0	67.0 - 149.0	81.0 - 169.0
	ALD 0.1	Number	49	48	49
		Mean ± SD	126.0 ± 20.3	121.0 ± 23.7	124.8 ± 18.3
		Median	129.0	123.5	124.0
		Range	63.0 - 164.0	54.0 - 192.0	75.0 - 158.0
	Placebo	Number	54	47	49
		Mean ± SD	129.4 ± 26.0	129.4 ± 27.7	134.6 ± 25.9
		Median	133.0	128.0	133.0
		Range	22.0 - 200.0	25.0 - 203.0	31.0 - 190.0

Cross-reference EOT Tables 79.A, and 80

Table 21

Study ALD-1537 Summary of Anti-Thrombin III and Protein C Levels
 (Data taken from sponsor's Table 10-18 Clinical Trial Report)

Table 10-18 Summary of Anti-Thrombin III and Protein C Levels
 (Safety Population)

Parameter			Week 0	Week 12	Week 24
Anti-thrombin III (%)	ALD 0.25	Number	51	52	52
		Mean ± SD	109.3 ± 9.7	105.0 ± 10.1	106.5 ± 9.4
		Median	108.0	104.5	107.0
		Range	89.0 - 134.0	82.0 - 135.0	89.0 - 132.0
	ALD 0.1	Number	49	48	49
		Mean ± SD	106.6 ± 9.7	101.4 ± 10.6	105.4 ± 9.1
		Median	108.0	101.0	105.0
		Range	79.0 - 125.0	63.0 - 120.0	83.0 - 122.0
	Placebo	Number	54	47	49
		Mean ± SD	107.9 ± 8.6	108.3 ± 8.6	108.9 ± 10.4
		Median	109.5	107.0	110.0
		Range	78.0 - 125.0	91.0 - 124.0	81.0 - 135.0
Protein C (%)	ALD 0.25	Number	51	52	52
		Mean ± SD	138.5 ± 22.6	129.0 ± 21.3	130.9 ± 21.4
		Median	140.0	125.0	126.0
		Range	87.0 - 226.0	81.0 - 185.0	78.0 - 187.0
	ALD 0.1	Number	49	48	49
		Mean ± SD	128.4 ± 20.9	122.3 ± 21.2	126.8 ± 20.7
		Median	129.0	121.0	128.0
		Range	74.0 - 171.0	62.0 - 166.0	59.0 - 175.0
	Placebo	Number	54	47	49
		Mean ± SD	136.0 ± 30.5	135.2 ± 29.8	135.9 ± 29.3
		Median	132.0	131.0	131.0
		Range	40.0 - 222.0	41.0 - 220.0	42.0 - 236.0

Cross-reference EOT Tables 84 and 88

Table 22

Study ALD-1537 Summary of Haemostatic Parameters
 (Data taken from sponsor's Table 10-19 Clinical Trial Report)

Table 10-19 Analysis of Changes in Haemostatic Parameters (Safety)

Parameter	Week	ALD 0.25 minus placebo		ALD 0.1 minus placebo	
		Treatment difference*	Confidence levels	Treatment difference*	Confidence levels
Fibrinogen	12	-0.28*	-0.45, -0.10	-0.35*	-0.53, -0.17
	24	-0.25	-0.45, -0.04	-0.17	-0.37, 0.04
Factor VII	12	-7.92*	-13.17, -2.68	-3.99	-9.39, 1.40
	24	-10.63*	-15.76, -5.50	-8.55*	-13.74, -3.35
Anti-thrombin III	12	-4.30*	-6.42, -2.18	-4.90*	-7.08, -2.73
	24	-4.03*	-6.47, -1.58	-3.56*	-6.03, -1.09
Protein C	12	-10.15*	-14.21, -6.09	-6.08*	-10.28, -1.89
	24	-9.25*	-13.51, -5.00	-5.03	-9.35, -0.70

*Statistically significant (p ≤ 0.018). *By analysis of covariance

Cross-reference EOT 1

Clinical Review

{William A. Lubas MD-PhD

{NDA 22-001, N 000}

{Activella 0.5mg/0.1mg (estradiol 0.5mg /noerthindrone acetate tablets 0.1mg)}

Breast Adverse Events

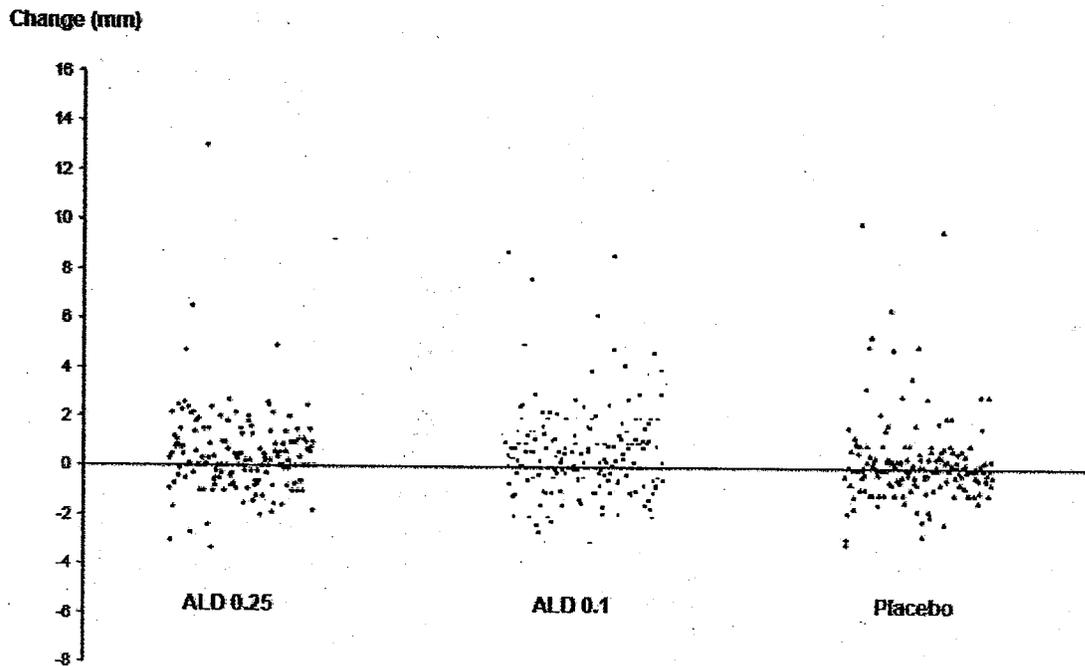
Clinically important symptoms relating to the breast (breast discomfort, breast pain and tenderness) were each reported by $\leq 2\%$ of subjects treated with Activelle _____, which was comparable with the placebo group. One subject in the ALD 0.25 treatment group was diagnosed with breast cancer after being treated for 173 days during the course of the trial. She had received hormone replacement products for 13 years prior to being enrolled in this study. So it is unlikely that the study drug was solely responsible for this adverse event. Mammographs were carried out on a subpopulation of 255 postmenopausal women from Nordic countries: Norway, Sweden, Denmark and Finland. Mammograms were performed prior to the start of treatment and after 6 months, using the same equipment at each assessment. The baseline mammogram was made during the screening period (it was also acceptable to use mammograms taken up to six months prior to trial entry) and the follow up mammogram was performed at the last visit or after at least five months of treatment. All patients who used systemic HRT up to two months prior to the screening mammogram were excluded from the analysis. At screening, mean breast density assessed by digitized quantification was 22.5%, 21.3% and 20.7% for ALD 0.25, ALD 0.1 and placebo, respectively. After 24 weeks of treatment the values were 23.9%, 21.1% and 21.4%, respectively. No overall treatment differences were detected between the treatment groups and placebo. Visual assessment according to the Wolfe classification and the percentage scale showed no increase in breast density after 24 weeks of treatment with Activelle _____. While this 6 month study showed no definite evidence of an increase in breast cancer risk or breast disease compared to placebo with this low dose estrogen formulation, it is not possible to extend these data to longer durations of therapy.

Endometrial Hyperplasia

The other major safety concern with this combination estrogen and progesterone drug product relates to whether there is sufficient progesterone in this low dose progesterone product to prevent estrogen induced endometrial hyperplasia. All subjects tested had normal Papanicolaou smear test findings at screening. At week 24 one subject each in the ALD 0.1 group (of 183; 1%) and the placebo group (of 178; 1%) had abnormal smear test findings. The incidence of endometrial thickening $\geq 5\text{mm}$ was 6% (11 subjects) in the ALD 0.25 group, 10% (19 subjects) in the ALD 0.1 group and 6% (8 subjects) in the placebo group. The distribution of endometrial thickness changes between the three treatment groups was very similar and changes primarily ranged between -2 mm and +2 mm with some cases occurring outside (above and below) these values.

Figure 2

**ALD-1537 Summary of Endometrial Thickness Changes
(Data taken from sponsor's Figure 10-1 Clinical Trial Report)**



The mean endometrial thickness values during the screening and final visits are summarized in Table 8. There was a slight increase in the mean endometrial thickness in all treatment groups over the course of the trial, increasing from 2.23mm to 2.65mm in the ALD 0.25 group, from 2.29mm to 2.87mm in the ALD 0.1 group and from 2.30mm to 2.56mm in the placebo group. The mean endometrial thickness during the screening visit as well as at the end of the trial was always within the normal postmenopausal range (< 5 mm) and is consistent with an adequate amount of progesterone in this combination drug product to prevent estrogen induced endometrial hyperplasia.

Table 8

**ALD-1537 Summary of Endometrial Thickness
 (Data taken from sponsor's Table 10-4 Clinical Trial Report)**

Table 10-4 Summary of Endometrial Thickness (mm) (Safety Population)

Treatment		Week 0	Week 24
ALD 0.25	Number	181	173
	Mean ± SD	2.23 ± 1.07	2.65 ± 1.64
	Median	2.00	2.40
	Range	0.00 – 4.90	0.00 – 13.00
ALD 0.1	Number	194	185
	Mean ± SD	2.29 ± 1.00	2.87 ± 1.82
	Median	2.10	2.50
	Range	0.00 – 4.80	0.00 – 12.00
Placebo	Number	200	177
	Mean ± SD	2.30 ± 1.06	2.56 ± 1.64
	Median	2.00	2.20
	Range	0.00 – 7.30	0.00 – 11.00

Cross-reference EOT Table 107

Endometrial biopsies were not a protocol-planned procedure conducted in the ALD-1537 trial. However, at the discretion of the investigators, 5 patients underwent endometrial biopsies (a total of five endometrial biopsies and four hysteroscopies were conducted during the trial) and all results were negative with regard to endometrial abnormalities. However, as mentioned previously these data cannot be extended to longer durations of therapy.

Common Adverse Events

Adverse events reported by ≥5% of the women in any treatment group are presented in sponsor's Table 23. The incidence of AEs seen with 0.1mg NETA (n=147, 76%) was slightly higher than seen in the placebo group (n=139, 70%). No AE was more common in the placebo group than in both NETA groups whereas the following AEs were more common in both NETA treatment groups compared to placebo e.g. vaginal hemorrhage (22 to 26% vs. 12%), headache (22 to 26% vs. 19%), nasopharyngitis (19 to 21% vs. 18%), back pain (6 to 10% vs. 4%), endometrial thickening (6 to 10% vs. 4%), and pharyngeal pain (4 to 5% vs. 3%) These AEs were not unexpected for postmenopausal women receiving estrogen replacement therapy.

Clinical Review

{William A. Lubas MD-PhD

{NDA 22-001, N 000}

{Activella 0.5mg/0.1mg (estradiol 0.5mg /noerthindrone acetate tablets 0.1mg)}

Table 23

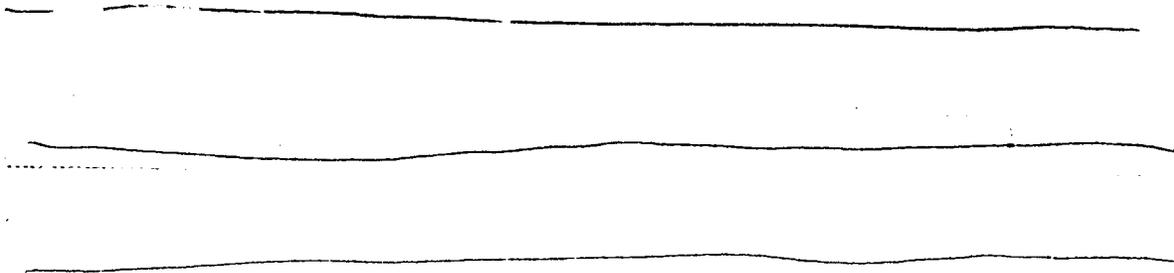
**Study ALD-1537 AEs occurring at $\geq 5\%$ in Any Treatment Group
(Data taken from sponsor's Table 10-9 Clinical Trial Report)**

**Table 10-9 Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of
Subjects (Safety Population)**

	ALD 0.25 (N=181) n (%) events	ALD 0.1 (N=194) n (%) events	Placebo (N=200) n (%) events
Number of subjects reporting AEs	127 (70) 571	147 (76) 673	139 (70) 520
Upper Abdominal Pain	9 (5) 11	5 (3) 6	7 (4) 12
Diarrhoea	3 (2) 3	11 (6) 13	11 (6) 13
Nausea	6 (3) 7	10 (5) 11	7 (4) 11
Arthralgia	9 (5) 18	6 (3) 9	5 (3) 5
Back Pain	11 (6) 16	20 (10) 20	8 (4) 9
Pain in Extremity	7 (4) 10	10 (5) 12	8 (4) 20
Headache	47 (26) 133	42 (22) 122	38 (19) 107
Endometrial Thickening	11 (6) 11	19 (10) 19	8 (4) 8
Nasopharyngitis	34 (19) 42	41 (21) 51	35 (18) 46
Pharyngolaryngeal Pain	9 (5) 11	7 (4) 7	6 (3) 6
Vaginal Haemorrhage	39 (22) 103	51 (26) 99	24 (12) 49

Cross-reference BOT Table 65

10.2 Line-by-Line Labeling Review



2 Page(s) Withheld

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 ✓ Draft Labeling

 Deliberative Process

Clinical Review

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{NDA 22-001, N 000}

{Activella 0.5mg/0.1mg (estradiol 0.5mg /noerthindrone acetate tablets 0.1mg)}

REFERENCES

Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. JAMA. Vol. 288, No. 3, 2002: 321-333

Crandall C., J, Women's Health 12(8):723-747, 2003. © 2003, Low-Dose Estrogen Therapy for Menopausal Women: A Review of Efficacy and Safety

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