CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-103

Medical Review(s)

Medical Officer's Review of NDA 21-103

1 General Information

1.1 NDA 21-103

1.2 Applicant: Novo Nordisk Pharmaceuticals
100 Overlook Center – Ste. 200
Princeton NJ 08540-7810
Contact: Lieselotte Bloss, D.V.M.
609-987-5852

1.3 Submission/review dates

1.3.1 Date of submission: 6/10/99

1.3.2 CDER stamp date: 6/11/99

1.3.3 Date submission received by reviewer: 6/24/99

1.3.4 Date review begun: 6/24/99

1.3.5 Dates (and summaries) of supplementary submissions:
11/23/99 (Submission of SAS data sets for clinical studies KLIM/PD/11/USA and KLIM/PD/4/F at request of FDA statistician, Japo Choudhury, Ph.D.)
12/22/99 (Submission of supplemental analyses of KLIM/PD/11/USA in response to comments and questions of Japo Choudhury, Ph.D.)
3/7/00 (Changes Being Effected Supplement for Activelle™ Name Change to Activella™)
3/24/00 (Safety Update: No serious adverse events reported from June 1, 1999 to March 20, 2000.)

1.3.6 Date review completed: 4/8/00

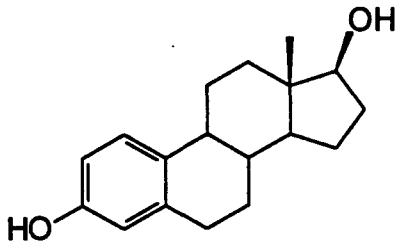
1.4 Drug Identification

1.4.1 Generic name: 17 β – estradiol (E_2) / norethindrone acetate (NETA) tablets

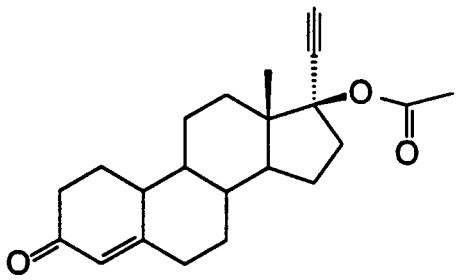
1.4.2 Proposed trade name: Activelle™; Activella™ (as of 3/7/00)

1.4.3 Chemical name: Estra-1,3,5(10)-triene-3,17β-diol / 17β-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one

1.4.4 Chemical structure:



17 β-Estradiol



Norethindrone Acetate

1.4.5 Molecular formula: $C_{18}H_{24}O_2$,1/2 H_2O / $C_{22}H_{28}O_3$
1.4.6 Molecular weight: 281.4 / 340.5 or 621.9 for combined product

1.5 Pharmacologic Category: Estrogen and Progestin

1.6 Dosage form: 1 mg estradiol / 0.5 mg norethindrone acetate

1.7 Route of Administration: oral
1.8 Proposed Indication and Usage : Prevention [redacted] of Postmenopausal Osteoporosis in Women with Intact Uteri

1.9 Proposed Dosage and Administration: 1 mg estradiol / 0.5 mg norethindrone acetate one tablet daily

1.10 Related Drugs: Estraderm transdermal system, conjugated (oral) estrogens, estradiol / norethindrone acetate (femhrt(r))

1.11 Material Reviewed: NDA 21-103 (73 volumes – particularly volumes 1,2,4,7-23), NDA 20-907 Medical Officer Review

1.12

Regulatory Background:
IND [redacted] submitted 7/15/93 to the Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580) for indication [redacted] prevention of osteoporosis
NDA 20-907 Activelle application approved 11/18/98 by the Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580) for treatment of moderate to severe vasomotor symptoms associated with the menopause, and vulvar and vaginal atrophy, in women with an intact uterus

Regulatory Recommendation:

The indication of prevention [redacted] of postmenopausal osteoporosis in women with an intact uterus is approvable, pending

1) adequate final sponsor responses to FDA questions;

2) change in labeling, as requested by FDA;
3) additional study of lower estradiol norethindrone acetate combination doses.

This review has been discussed with Drs. Japo Choudhury (statistician), Eric Colman (Osteoporosis Team Leader), Saul Malozowski (Diabetes Team Leader), and Phil Price (Medical Reviewer, HFD-580) and Randy Hedin (CSO).

Abbreviations are defined in the text and also below:

Activelle (in this review) = Activella = 17 β – estradiol (E_2) 1 mg/ norethindrone acetate (NETA) 0.5 mg

AE = adverse events; **A-P** = anteroposterior; **BMD** = bone mineral density; **DEXA** = x-ray absorptiometry for assessment of bone mineral density; **E_2** = 17β - estradiol; **EE** = ethinyl estradiol; **ERT** = estrogen replacement therapy; **FSH** = follicle stimulating hormone; **HRT** = hormone (estrogen+progestin) replacement therapy; **ITT** = intent to treat analysis; **LOCF** = last observation carried forward or endpoint, referring to statistical analysis; **NDA** = New Drug Application; **NETA** = norethindrone acetate; **qd** = daily; **qhs** = daily at bedtime; **RCT** = randomized clinical trial; **TVS** = transvaginal ultrasound; **u**-hydroxyproline=urinary hydroxyproline; **u**-pyridinoline = urinary pyridinoline; **US** or **USA** = United States of America

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3 Financial Disclosure

The sponsor has included an approved form "Certification: Financial Interests and Arrangements of Clinical Investigators" (OMB No. 0910-0396), signed by the vice-president for regulatory affairs. In this form, the sponsor certifies that the sponsor has "not entered into any financial arrangements with the listed clinical investigators [24 principal and 59 sub investigators for KLIM/PD/11/USA are listed] whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)....that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests....that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

4 Summary

NDA 21103 (Activelle, Novo Nordisk) has been submitted as a Type 6 NDA for approval of one fixed continuous combination of 17β-estradiol (E_2) 1 mg / norethindrone acetate (NETA) 0.5 mg for the prevention and [redacted] postmenopausal osteoporosis in women with an intact uterus. This drug at this dosage has been previously approved in the Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580) (NDA 20-907, 11/18/98) for treatment of moderate to severe vasomotor symptoms associated with the menopause, and vulvar and vaginal atrophy, in women with an intact uterus.

Two multicenter, randomized, double-blind, controlled 2-year studies were conducted for the postmenopausal osteoporosis indication and are the main focus of this review. In the United States study (KLIM/PD/11/USA), 20 investigators at 17 centers participated. The study population comprised 333 postmenopausal nonosteoporotic women with intact uteri, who were randomized to seven treatment arms (E_2 0.25 mg, E_2 0.5 mg, E_2 1.0 mg, E_2 1mg + NETA .25 mg, E_2 1mg + NETA 0.5 mg, E_2 2 mg + NETA 1 mg, placebo). In the European study, four centers in France (KLIM/PD/4/F), the study population comprised 135 postmenopausal nonosteoporotic women (122 or 90% of whom had intact uteri), who were randomized to three treatment arms (E_2 1mg + NETA .25 mg, E_2 1mg + NETA .5 mg, placebo). Thus a total of 93 postmenopausal women were exposed to E_2 1mg + NETA .5 mg (Activelle) in the two-year studies.

A statistically significant change in the primary efficacy variable – anteroposterior view lumbar spine bone mineral density (BMD) by x-ray absorptiometry (dexa scan) as compared to placebo was noted in all the treatment groups in both studies. Changes in secondary efficacy variables (BMD femoral trochanter, and biochemical markers of bone turnover in both studies; BMD femoral neck in US study; in addition, BMD distal radius and BMD total body in the European study;) confirmed the preservation of bone and prevention of osteoporosis suggested by the primary efficacy variable. In addition, the sponsor presents three supportive 24-week studies, primarily for the safety data. The addition of the progestin norethindrone acetate to estradiol significantly reduces the incidence of endometrial hyperplasia (from 14% for estrogen alone to <1% for the estrogen/progestin combinations) in these studies. However, breast pain and postmenopausal bleeding were frequent adverse events in the E_2 1mg + NETA 0.5 mg (Activelle™) group and resulted in withdrawal of 6 and 11% (breast pain) and 6 and 4%

(postmenopausal bleeding) of subjects during the two-year US and European studies, respectively. These adverse events are particularly worrisome in the postmenopausal population because of the increased risk of malignancy, including breast cancer and endometrial cancer in this age group, and the increased anxiety, medical interventions, and health care costs that may ensue from the adverse events.

The Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women, published in 1995 *after* these studies were initiated, states "Approvals of specific fixed dose estrogen/progestin HRT products for estrogen class labeling indications will be based on the combination drug policy (see 21 CFR 300.50) and the determination, within reasonable limits, that a combination drug contains the lowest effective dosages of each of its active components for their respective labeled indications." Based on the data from the USA two year study, E_2 1mg + NETA 0.5 mg (Activelle™) is not the lowest effective dose for prevention of osteoporosis, and lower dose(s) of E_2 and NETA (e.g., E_2 0.5 mg + NETA 0.25 mg, E_2 0.5 mg + NETA 0.5 mg, E_2 0.25 mg + NETA 0. 5mg, or E_2 0.25 mg + NETA 0.25mg) may result in adequate osteoporosis prevention with less estrogen-related events, particularly postmenopausal bleeding and breast pain. Of note, as per the draft Osteoporosis Guideline (April 1994), the outcome of these two pivotal estrogen osteoporosis studies has been BMD and not fracture. It is not known if a lower dose of combined, continuous E_2 NETA therapy will translate to fracture prevention as well as prevention of osteoporosis.

Because of the safety concerns associated with a relatively high dose of estrogen for osteoporosis prevention, E_2 1mg + NETA 0.5 mg (Activelle™) is approvable for prevention of osteoporosis only with the following qualifications: (1) a dose ranging, two-year study evaluating several lower dose combinations of estradiol and norethindrone, including a noneffective combination dose, should begin promptly, with plans for a one-year interim analysis. (2) the label must include the lowest estradiol norethindrone acetate combination for osteoporosis protection based on BMD preservation. At the very least, the label must indicate that the doses of estradiol and norethindrone acetate in the combination product Activelle™ may not be the lowest effective doses for the prevention of osteoporosis.

5 Chemistry/Manufacturing Controls

Chemistry data were previously submitted in NDA 20-907. Additional information was submitted in this NDA, and it is being reviewed by the chemist (Sheldon Markofsky, Ph.D.).

6 Animal Pharmacology/Toxicology

No preclinical data were submitted in this NDA. Only limited preclinical data were submitted in NDA 20-907.

7 Microbiology

No microbiology studies were submitted.

8 Human Pharmacokinetics/Pharmacodynamics

A food effect was noted in NDA 20-907 on the bioavailability of norethindrone (19% increases in AUC_{0-72} and 36% decreases in C_{max}) but not on the bioavailability of estradiol.

No new biopharmaceutic, pharmacokinetic, drug metabolism, pharmacodynamic, or clinical pharmacology information was submitted in this NDA. Previously submitted information was reviewed in HFD-580 and found acceptable. The clinical pharmacology reviewer, Ron Kavanagh, Ph.D., noted the lack of information in the elderly, the population expected to use this medication, and the relevant comments in the GERIATRIC USE section of the label: "*Clinical studies of Activelle did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.*" (21 CFR 201.57 (10)(ii)(A) Dr. Kavanagh noted that additional pharmacokinetic studies were not warranted, as they would not be expected to alter the labeling.

9 Human Clinical Experience

Prior US Experience

The combination of estradiol 1 mg norethindrone acetate 0.5 mg tablets or Activelle ™ has been approved in USA as continuous combined estrogen progestin therapy for menopausal symptoms since 11/18/98 but this product has not been marketed in the USA. The table below summarizes the main clinical studies that were submitted for review for the postmenopausal symptoms indication.

Pivotal Clinical Studies for Approval of Activelle (NDA 20-907) for Postmenopausal Symptoms
(Summarized by Medical Officer from Medical Officer Review by Phil Price, M.D., 11/98)

Protocol	KLIM/PD/8/USA	KLIM/PD9/USA	KLIM/PD/7/USA
Design	Multicenter, randomized, double-blind	Multicenter, randomized, double-blind	Multicenter, randomized, double-blind
Duration	12 weeks	12 weeks	12 months
Treatment arms	E_2 0.25 mg E_2 0.5 mg E_2 1 mg E_2 2 mg placebo	E_2 1 mg E_2 1 mg NETA 0.5 mg placebo	E_2 1 mg E_2 1 mg NETA .1 mg E_2 1 mg NETA 0.25mg E_2 1 mg NETA 0.5 mg

Sample size • **Screened** • **Randomized** • **Completed**	 594 333 280	 224 92 90	 1176 925
Inclusion criteria • **Age** • **Flushes** • **Endometrial Thickness** • **17β–E_2 (pg/ml)** • **FSH (miu/ml)** • **Amenorrhea** • **Prior HRT** • **Prior ERT**	• Postmenopausal women with intact uterus • 40-60 years • moderate-severe flushes • endometrial thickness < 5mm (by TVS) • 17β–$E_2 \leq 20$ pg/ml • FSH≥50 miu/ml • amenorrhea ≥ 6 months	• Postmenopausal women with intact uterus • 40-60 years • moderate-severe flushes • endometrial thickness < 5mm (by TVS) • 17β–$E_2 \leq 20$ pg/ml • FSH≥50 miu/ml • amenorrhea ≥ 6 months • no prior HRT ≥ 8wks • no prior ERT ≥ 12 wks	• Postmenopausal women with intact uterus • ≥45 years • endometrial thickness < 4mm (by TVS) • 17β–$E_2 \leq 25$ pg/ml • amenorrhea ≥ 12 months • no prior HRT ≥ 8wks • no prior ERT ≥ 12 wks
Primary efficacy	Mean change in number of moderate-severe hot flushes per week **Results:** significant for 1 and 2 mg E_2 doses (4-12 wks); for .5 mg E_2 (8-12 wks)	Mean change in number of moderate-severe hot flushes per week **Results:** significant for 1 mg E_2 doses and more significant for 1 mg E_2 0.5 mg NETA (4-12 wks) when compared to placebo	Endometrial hyperplasia **Results:** E_2 1 mg 13.8% E_2 1 mg NETA .1 mg 0.8% (1 complex, 1 simple) E_2 1 mg NETA 0.25mg 0.4% (complex) E_2 1 mg NETA 0.5 mg 0.4% (simple)
Secondary efficacy			Endometrial histology Endometrial thickness Bleeding/spotting (cumulative) 30.4, 24.3, 19, 13.8% amenorrhea (days) 259, 273, 266, 269
Safety	Treatment-emergent AEs higher in 2mg; Postmenopausal bleeding, headache, breast pain; Endometrial hyperplasia: P (1 complex endometrial hyperplasia), .5 mg (1 complex endometrial hyperplasia + atypia), 1 mg (1 simple hyperplasia), 2 mg (7 complex hyperplasia)	Treatment-emergent AEs (Postmenopausal bleeding, headache, breast pain) higher in 1 mg E_2 0.5 mg NETA; Amenorrhea: (P,E_2,E_2NETA) 79, 72, 48% bleeding/spotting 3, 7, 24 % endometrial hyperplasia 0, 4, 0% proliferative endometrium 17, 58, 4 %; 2 ovarian cysts in E_2NETA	7 cases malignant breast neoplasm distributed among treatment groups

Abbreviations: **AE** = adverse event(s); **E_2** = 17β - estradiol; **ERT** = estrogen replacement therapy; **FSH** = follicle stimulating hormone; **HRT** = hormone (estrogen + progestin) replacement therapy; **NETA** = norethindrone acetate; **TVS** = transvaginal ultrasound

Thus, both the E_2 .5 mg and E_2 1mg doses decreased the frequency of hot flushes at 8-12 weeks and 4-12 weeks, respectively, with the lower estradiol dose having a slower onset. Addition of NETA (.1, .25, and .5 mg) to 1 mg of E_2 decreased the frequency of endometrial hyperplasia from 13.8% (for E_2 alone) to 0.8, 0.4, 0.4%, respectively, and decreased bleeding and spotting from 30.4 (for E_2 alone) to 24.3, 19, and 13.8%, respectively. Thus 1 mg E_2 .5 mg NETA was selected as the optimal continuous combination dosage for the treatment of postmenopausal symptoms. However, it must be emphasized that the level of scrutiny of adverse events must be more stringent for a more chronic indication (e.g., osteoporosis prevention) than for a more relatively limited indication (e.g., postmenopausal symptoms).

Foreign Experience

The combination of estradiol 1 mg norethindrone acetate 0.5 mg tablets or Activelle ™ has been approved in Europe for the menopausal symptoms indication since 1998 and has been marketed in ten European countries. It was approved in Norway (1/8/99) for both menopausal symptoms and osteoporosis indications.

Post-Marketing Experience

As of 11/4/98, the sponsor reports that Activelle was available in three countries, Sweden, Germany, and United Kingdom; [redacted] had been sold; and no spontaneous adverse events had been reported to Novo Nordisk. An update of WHO postmarketing data for Activelle has been requested from the FDA post-marketing division. However, a passive post-marketing surveillance system may not adequately assess the adverse events of a drug product, particularly a drug product that is not the first in its class.

10 Clinical Studies

Indication: Prevention [redacted] of Postmenopausal Osteoporosis

The objective or rationale, study design, population, procedures, evaluability criteria and defined clinical endpoints and statistical considerations for the two two-year osteoporosis studies and the three 24-week supportive safety studies are summarized in the following paragraph and the tables in this section.

Two multicenter, randomized, double-blind, two-year studies (one performed in the USA - KLIM/PD/11/USA and one performed in France - KLIM/PD/4/F) with primary endpoints of change in lumbosacral spine bone mineral density (BMD) and secondary endpoints of change in hip bone mineral density (BMD) and change in concentration of biochemical markers of bone

turnover were conducted in healthy nonosteoporotic [i.e., normal bone density by the current World Health Organization definition] postmenopausal women mostly with intact uteri (327/327 in US study; 122/135 or 90% in the French study). In the US study, three doses of E_2 alone (E_2 0.25 mg, E_2 0.5 mg, E_2 1 mg), and three combination E_2 NETA doses (E_2 1 mg NETA 0.25 mg, E_2 1 mg NETA 0.5 mg [Activelle], E_2 2 mg NETA 1 mg) were compared to placebo. In the French study, two combination doses of E_2 NETA (E_2 1 mg NETA 0.25 mg, E_2 1 mg NETA 0.5 mg [Activelle]) were compared to placebo. Calcium was supplemented (1000 mg and 500 mg, respectively, in the two studies), but no vitamin D was administered. Of note, drug therapy was potentially administered with food in the French study (given qd) but less likely in the US study (given qhs). The design, sample sizes, inclusion and exclusion criteria, efficacy and safety measures, and statistical analyses of these studies are summarized in the table below.

NDA 21-103 Clinical Studies of Activelle Efficacy and Safety for Prevention of Postmenopausal Osteoporosis
(Summarized per Medical Officer)

Protocol	KLIM/PD/11/USA (pivotal-Phase 3)	KLIM/PD/4/F (France) (pivotal-Phase 3)
Design	Multicenter (17), randomized, parallel, double-blind (10 visits)	Multicenter (4), randomized, parallel, double-blind (7 visits + 3 telephone conversations)
Duration	26 lunar (28 d) months (9/28/95-7/19/98)	24 months (9/29/94-4/10/98)
Treatment arms	E_2 0.25 mg E_2 0.5 mg E_2 1.0 mg E_2 1mg + NETA .25 mg E_2 1mg + NETA 0.5 mg E_2 2 mg + NETA 1 mg placebo (administered qhs as single tablet) Calcium 1000 mg/day (all groups)	 E_2 1mg + NETA .25 mg E_2 1mg + NETA 0.5 mg placebo (administered qd as single tablet) Calcium 500 mg/day (all groups)
Sample size • **Planned** • **Screened** • **Randomized** • **Completed** • **Analyzed**	 320 737 327 [47 on Activelle] 189 (58%) 327 (actual ITT population) 258 (modified ITT per sponsor) 184 (completers) 171 (per protocol)	 120 215 135 [46 on Activelle] 91 (67%) 135 (actual ITT population) 115 (modified ITT per sponsor) 91 (completers) 73 (per protocol)

Inclusion criteria • **Population** • **Age** • **Time from menopause** • **BMD lumbar spine t-score** • **Plasma E_2 (pg/ml)** • **Plasma FSH (miu/ml)** • **Endometrial Thickness** (See also Appendix of Medial Officer's Review.)	• Postmenopausal women with intact uterus • ≥45 years • 1-5 years since last menses • BMD lumbar spine t-score >-2 SD of healthy young adult women (>0.827gm/ cm^2 for Hologic or > 0.940 gm/cm^2 for Lunar DEXA systems) • ≤20 • ≥40 • ≤ 6mm (pelvic ultrasound with vaginal probe)	• Postmenopausal women (n=122 with intact uterus) (n=13 post hysterectomy: E2/NETA .25 6 E2/NETA .5 3 Placebo 4) • 45-65 years • > 1 year since last menses • BMD lumbar spine t-score between -1.9 and +2.0 SD of healthy young adult women (0.80 g/cm^2 ≤ BMD L_{1-4} ≤ 1.20 g/cm^2) • ≤30 • >40 • ≤ 4mm (transvaginal ultrasound)
Exclusion criteria (See also Appendix of Medical Officer's Review.)	osteoporosis MI in past 6 months Hx CVA or thrombophlebitis Diabetes Mellitus >30% above IBW smoking >20 cig/day SBP>160 mmHg DBP>100 mmHg Chronic corticosteroid therapy Prior fluoride, calcitonin, bisphosphonate therapy for >14 days Estrogen use within 6 months of initial visit	Osteoporosis and osteoporotic fractures Hx CHF, MI, angina,arrhythmia Hx CVA or thrombophlebitis Diabetes Mellitus BMI > 30 kg/m^2 Smoking >40 cig/day SBP>170 mmHg DBP>100 mmHg Renal Failure Estrogen, progesterone, calcitonin, fluoride, biphosphonate, corticosteroid washout < 6 months
Primary efficacy	BMD lumbar spine (A-P view, L1-4) Percent change from baseline (BMD measured at baseline, 13,19,26 months)	BMD lumbar spine (A-P view, L1-4) Logarithm of BMD spine at end of study (for each subject) divided by BMD at baseline (BMD measured at baseline, 6, 12, 18, 24 months)
Secondary efficacy	BMD femoral neck BMD femoral trochanter Percent change from baseline (BMD measured at baseline, 13,19,26 months) Biochemical markers of bone turnover (at 3,6,13,19,26 months)	BMD femoral neck BMD femoral trochanter BMD Ward's triangle BMD distal radius BMD total body (BMD measured at baseline, 6, 12, 18, 24 months) Biochemical markers of bone turnover (at ? 3,6,12,18,24 months)

Safety	Physical and gynecologic exams Vital signs Mammography Endometrial biopsy Vaginal ultrasound Pap smear Routine blood and urine laboratory tests Hormone levels (E_2 E_1S FSH) Adverse Events	Plasma lipids Postmenopausal bleeding (daily diary record) FSH E_2 Endometrial thickness Vital Signs Adverse Events
Statistical analysis	• Demographic and baseline variables for the 7 groups compared by descriptive statistics at baseline • Comparison of individual active doses with placebo using ANOVA or ANCOVA	• Comparison of treatment groups with respect to logarithm of BMD spine (at last visit for each subject) divided by BMD spine at baseline, in normal regression model, with covariates (osteocalcin, u-hydroxyproline, u-pyridinoline Type I collagen C-telopeptide, baseline BMD, BMI, menopausal age, center) – two-sided t-test • Pairwise comparison of each active treatment group and placebo

In addition, the sponsor presents three 24-week studies (KLIM/PD/18/J (Japan), KLIM/PD/19/USA, KLIM/PD/15/IRL (Ireland)) as supportive safety data. The Japanese study also had BMD as a primary outcome, while the other two studies had lipids as primary outcomes. The small sample size of the Japanese study (only 16 subjects were randomized to Activelle) and the short duration (24 weeks) limit contribution of this study to support the efficacy of E_2 1 mg NETA 0.5 mg [Activelle]. Of note, the populations in these studies comprised approximately 30% of women who had undergone hysterectomies (14/47, 82/270, 11/38 in the three studies, respectively) and thus there was a relatively smaller possible data set regarding endometrial hyperplasia and postmenopausal bleeding.

Additional NDA 21-103 Clinical Studies of Activelle Safety for Prevention of Postmenopausal Osteoporosis
(Summarized per Medical Officer)

Protocol	KLIM/PD/18/J (Japan) (supportive- Phase 2)	KLIM/PD/19/USA (supportive – Phase 2/3)	KLIM/PD/15/IRL Ireland (supportive – Phase 2)
Design	Multicenter (19), randomized, single-blind	Single-center, randomized, double-blind, placebo-controlled	Single-center, randomized, double-blind
Duration	24 weeks (9/4/95 – 12/5/97)	24 weeks (6/5/96-3/31/97)	6 lunar months (1/3/96-7/29/97)
Treatment arms	E_2 1 mg + NETA 0.5 mg, E_2 2 mg + NETA 1 mg, placebo Calcium 800 mg/day (all groups)	E_2 1 mg E_2 1 mg + NETA 0.25 mg $E_2$1 mg + NETA 0.5 mg placebo	E_2 1 mg E_2 1 mg + NETA 0.5 mg
Sample size • **Planned** • **Screened** • **Randomized** • **Completed**	 47 (16 on Activelle) 41	 260 498 270 (67 on Activelle)	 42 38 (19 on Activelle) 35
Inclusion criteria • **Population** • **Age** • **Time from menopause** • **BMD lumbar spine t-score** • **Plasma E_2 (pg/ml)** • **Plasma FSH (miu/ml)**	• Postmenopausal women (n=33 with intact uterus, (n= 14 post hysterectomy E2 1/NETA .5 1 E2 2/NETA 1 5 Placebo 4) • 30-64 years • 1 yr since menses • BMD lumbar spine t-score <-1.5 SD of healthy young adult women	• Postmenopausal women (n=188 with intact uterus, n=82 Post hysterectomy E2 23 E2 1/NETA .25 18 E2 1/NETA .5 21 Placebo 20 • 42-70 years (mean 58) • 1 yr since menses • E2 <20 pg/ml	• Postmenopausal women (n=27 with intact uterus, n=11 Post hysterectomy E2 8 E2 1/NETA .5 3 • 45-70 (mean 63) • >1 yr since menses • Type 2 Diabetes Mellitus on diet ± oral hypoglycemic agent • E2<50 • FSH≥40 miu/ml
Primary efficacy	BMD lumbar spine (BMD measured at 12 and 24 weeks)	LDL-cholesterol	LDL-oxidisability
Secondary efficacy	Presence of fracture Biochemical markers of bone turnover	Other Lipoproteins Insulin Glucose HbA1c C-peptide Fibrinogen Homeostatic profile TGF-β	Lipoproteins LDL-fatty acids triglycerides

Safety	Physical and gynecologic exams Vital signs Clinical laboratory tests Adverse events E_2 E_1 FSH SHBG	Physical and gynecologic exams Vital signs Mammography Pelvic ultrasound and/or endometrial biopsy Vaginal cytology Cliniccal laboratory tests Adverse events	Endometrial biopsy endometrial thickness Bleeding clinical lab tests Adverse events

A total of 817 postmenopausal women were enrolled in these 5 clinical trials, with 195 exposed to E_2 1 mg NETA 0.5 mg [Activelle]. Of these 195 women, 93 (48%) were enrolled in the two year trials. The number of subjects randomized to the treatment groups in the five studies discussed in this NDA are summarized in the sponsor's table below:

Extent of Exposure

			Unopposed E_2 (mg)				E_2 + NETA (mg)			
		Placebo	0.25	0.50	1.0	2.0	1+0.25	1+0.50	2+1	Total
11/USA	2 years	48	45	44	46	-	49	47	48	327
4/F	2 years	45	-	-	-	-	44	46	-	135
18/J	6 months	16	-	-	-	-	-	16	15	47
19/USA	6 months	68	-	-	67	-	68	67	-	270
15/IRL	6 months	-	-	-	19	-	-	19	-	38
TOTAL		177	45	44	132	-	161	195	63	817

1 mg E_2 + 0.5 mg NETA: Activelle

The specific biochemical markers of bone turnover studied in the three clinical studies with BMD as the primary efficacy are outlined in the sponsor's table below:

Resorption and Formation Markers Assessed in the Efficacy Trials

	11/USA	4/F	18/J
Resorption			
U-pyridinoline crosslinks Type I collagen C-telopeptide	-	x	x
U-pyridinoline	x	-	x
U-deoxypyridinoline	x	-	x
Formation			
serum osteocalcin	-	x	x
serum bone-specific alkaline phosphatase	x	x	x
serum C-terminal propeptide of type I collagen	-	x	-

Statistical Considerations

The definitions of the populations analyzed differed somewhat for the two osteoporosis two-year studies:

Populations Analyzed		
	KLIM/PD/11/USA	KLIM/PD/4/F
ITT	For safety data – all randomized	Took one dose of trial product
Modified ITT	BMD- baseline and 1 post-randomization	BMD- baseline and 1 post-randomization
Per Protocol	Complete ≥ 24 lunar months; Visit 10 data; Meet certain inclusion/exclusion criteria: Normal BMD, no osteoporosis or other bone disease, no osteoporotic fractures, no immobilization, no fluoride, calcitonin, bisphosphonates, no ERT/HRT within 6 months	Completed trial; 80 % compliance; met inclusion/exclusion criteria

The power considerations were the same for both clinical trials: detect 4% difference in BMD between treatment groups and placebo, with 90% power at a 5% level of significance. Multiple treatment comparisons were not taken into consideration.

The sponsor's analyses for the primary efficacy variable, percent change in lumbar spine (L1-L4) bone mineral density, in the two two-year studies include the following:

1) Intent to treat analysis with last observation carried forward (ITT,LOCF);
2) A completer analysis;
3) Two responder analyses, based on the ITT,LOCF, and two definitions of response: percentage change > 0 or >2%.
4) A subset analysis where "normal" lumbar spine BMD is defined as t score > -1 SD and "low" BMD is defined as –2 < t score < -1 SD.

   These definitions of "normal" and "low" BMD are misleading , as the currently used definition of normal bone density proposed by the World Health Organization defines normal bone mineral density as a t score > -2.5 SD (i.e., 2.5 standard deviations below the mean for young white adult women.) More correctly, these subsets represent normal and low normal BMD.

According to ICH guideline E9 "Statistical Principles for Clinical Trials," the most important analysis is the intent to treat analysis with the last observation carried forward. In KLIM/PD/11/USA, however, the sponsor included only those subjects with a post-baseline BMD measurement in the ITT analysis. Thus, about 20% of the randomized subjects were not included. To verify the sensitivity of this ITT analysis, the FDA statistician imputed the mean Activelle-observed change in the placebo cases with missing subsequent data and the mean placebo-observed change in the Activelle subjects with missing data. This imputation was a worst case scenario. He also requested that the sponsor perform an imputed model analysis. Both the FDA and subsequent sponsor analyses confirmed the submitted ITT efficacy analyses. The sponsor's completer analyses also supported the ITT (LOCF) analysis. Since the ITT

analysis is the primary analysis the FDA recommends, only the results from the ITT analyses are included in the Results section. The supportive completer and responder analyses are summarized in the Appendix of the review.

In the report of KLIM/PD/11/USA, the sponsor reports that an administrative decision was made to market only one estradiol norethindrone acetate combination (E_2 1 mg NETA .5 mg) in the US. Treatment codes were unblinded while seven women were receiving treatment. Since only data collected prior to the unblinding were included in the analyses, the sponsor also performed the supplementary analyses which included the data for these seven subjects after unblinding. These additional analyses were confirmatory.

Study Results

Unless it is stated that the data in a table were summarized by the medical officer, the tables and figures in the results section are reproduced from the Integrated Summary of Efficacy and the Integrated Summary of Safety in NDA 21103. As noted above, since the ITT analysis is the primary analysis the FDA recommends, only the results from the ITT analyses are included in the Results section. The supportive completer and responder analyses are summarized in the Appendix of the review.

Demographics, Evaluability

A total of 462 healthy postmenopausal women with normal bone mineral density were randomized in the two two-year osteoporosis trials. They were predominantly Caucasian (92%) in the US trial, with 2% Blacks, 1% Orientals, and 4% other. (Race was not listed in the French trial.) The mean age was 53 in the US trial and 58 in the French trial; the former group was approximately three years postmenopausal while the latter group was nine years postmenopausal. The weight was somewhat higher in the US population (mean range 67-70 kg vs. 60-64 kg in the French study). All the women in the US trial had an intact uterus, and 16 % were oophorectomized; 90% of the French women had an intact uterus and none of these were oophorectomized. Only 4-9% of the women in the US trial reported prior estrogen use, while 22-38% of the women in the French trial did. There were no baseline statistical differences among the treatment groups.

Subject Disposition – KLIM/PD/11/USA
(Summarized by Medical Officer)

Treatment Group	Placebo	E2 0.25 mg	E2 0.5 mg	E2 1 mg	E2 1 mg NETA .25mg	E2 1 mg NETA .5mg	E2 2 mg NETA 1mg	Total
# Randomized	48	45	44	46	49	47	48	327
# ITT (LOCF) BMD spine analysis	37	37	31	37	37	37	42	258 (79%)
# Completers	28	25	24	22	30	24	31	184 (56%)
# Premature Discontinuations								

Adverse Events	11 (23%)	9 (20%0	6 (14%)	16 (35%)	7 (14%)	8 (17%0	8 (17%)	65 (20%)
*Noncompliance	6 (12%)	7 (16%)	8 (18%)	6 (13%)	6 (12%)	5 (11%)	6 (12%)	
**Administrative	2 (4%)	4 (9%)	6 (14%)	4 (9%)	5 (10%)	6 (13%)	2 (4%)	

Numbers refer to number of women (not events).
*Number of women discontinued secondary to noncompliance and administrative reasons were calculated form the percentages presented in the NDA table.
**This category includes 7 women who were still on treatment when the study was unblinded. Due to "administrative reasons" which were not specified in the NDA, the sponsor unblinded the treatment codes on 5/20/98 while 7 women were still receiving treatment. Only data collected prior to 5/20/98 were included in the efficacy analyses. At the request of the FDA statistician, analyses including these data were submitted in a supplement and there were no significant differences in the results.

In KLIM/PD/11/USA, compliance with study drug and scheduled visits was required. If a subject missed more than 5 tablets per lunar month, she was withdrawn due to non-compliance. The median percentage of missed calcium tablets was 4 to 10% in the different treatment groups (range 0-100%). No statistical tests were reported.

Concomitant medically necessary prescription and over-the-counter medications, including analgesics, antibiotics, decongestants, laxatives, and vaccines, were permitted. Non-topical steroids (escept study preparation), vaginal preparations containg estrogen, drugs affecting estrogen metabolism (barbiturates, rifampicin, phenytoin, carbamazepine), fluoride, calcitonin, bisphosphonates and vitamin D metabolites were excluded.

The most common protocol violations listed were missing the 26 month BMD data and the exclusion criterion of estrogen use within 6 months of baseline visit. A total of 18 subjects violated the estrogen exclusion criterion:

Treatment Group	Placebo	E2 0.25 mg	E2 0.5 mg	E2 1 mg	E2 1 mg NETA .25mg	E2 1 mg NETA .5mg	E2 2 mg NETA 1mg	Total
# women using estrogen < 6 months before baseline	4	2	2	0	4	2	4	18

Since they are distributed among all groups, it is less likely that this violation biased the ITT analysis.

Sponsor's Table: Baseline Characteristics - KLIM/PD/11/USA .

	Placebo	E_2 (mg)			E_2 + NETA (mg)		
		0.25	0.5	1	1 + 0.25	1 + 0.5 (Activelle)	2 + 1
Randomized	48	45	44	46	49	47	48
Age (years)	53.5 ± 3.5	53.2 ± 3.9	52.3 ± 3.7	52.7 ± 3.6	52.4 ± 3.9	52.5 ± 4.1	53.1 ± 3.4
TSM (years)	3.1 ± 1.3	3.1 ± 1.5	2.5 ± 1.2	2.6 ± 1.2	2.8 ± 1.3	3.1 ± 1.3	2.8 ± 1.2
BMI (kg/m^2)	25.2 ± 3.7	27.1 ± 3.6	25.8 ± 4.0	25.5 ± 3.6	25.6 ± 3.8	25.3 ± 3.7	25.1 ± 3.8
BMD, spine *	1.09 ± 0.15	1.10 ± 0.15	1.07 ± 0.14	1.09 ± 0.14	1.09 ± 0.16	1.11 ± 0.15	1.05 ± 0.12
Low **, N	15	9	17	16	13	14	19
Normal *** , N	33	36	27	30	36	33	29

TSM: time since menopause; BMI: body mass index; BMD: bone mineral density;
* BMD: bone mineral density, lumbar spine (g/cm^2)
** Low: low bone mass (t-score <-1 SD of the mean for healthy adult women)
*** Normal: normal bone mass (t-score >-1 SD of the mean for healthy adult women)
Data are presented as mean ± SD

As noted above, these definitions of normal and low BMD are misleading, as all subjects had normal BMD by WHO criteria.

Subject Disposition – KLIM/PD/4/F
(Summarized by Medical Officer)

Treatment Group	Placebo	E2 1 mg NETA 0.25 mg	E2 1 mg NETA 0.5 mg	Total
# Randomized	45	44	46	135
# ITT (LOCF) BMD spine analysis	40	37	38	115 (85%)
# Completers	33	29	29	91 (67%)
# Premature Discontinuations				
Adverse Events	6 (13%)	11 (25%)	13 (28%)	30 (22%)
*Noncompliance	0 (0%)	1 (2%)	2 (4%)	
*Administrative	6 (13%)	3 (7%)	2 (4%)	

Numbers refer to number of women (not events).
*Number of women discontinued secondary to noncompliance and administrative reasons were calculated form the percentages presented in the NDA table.

In KLIM/PD/4/F, compliance with the study drug and calcium was assessed by history, examinations of returned calendar packs, and bleeding diaries. Noncompliance was defined as missing > 5 tablets per month; the subject would be excluded from the per protocol analysis. Sixteen subjects took excluded drugs during the trial: 14 took progestogen for breast pain (3 in the placebo group, 5 in E2 1mg NETA .25 mg and 6 in E2 1 mg NETA .5 mg), one took topical estrogen for valvulitis (she had also taken progestogen) (placebo), one took prednisone for 1.5 months (E2 1mg NETA 0.25 mg), and one took carbamazapine for 3 weeks and calcitonin for the pain of ankle fracture for one week (placebo). Thus, these violations would not be expected to unduly bias efficacy. Of the 42 protocol violations listed by the sponsor, the majority (17)

related to the omission or delay of study drug use, and were distributed among the three groups. Other listed protocol violations (mostly administrative – e.g., omission of laboratory tests or informed consent, or slightly higher baseline E_2) were also unlikely to bias the results. Data was assessed to be adequate with minor violations in the two KLIM/PD/11/USA sites [L. Cohen MD, (Sarasota FL) randomized n = 40; M. Greenwald MD (Palm Springs CA) randomized n = 24) selected by the FDA Division of Scientific Investigation for inspection.

Sponsor's Table. Baseline Characteristics - KLIM/PD/4/F

	Placebo	1 mg E_2 + 0.25 mg NETA	1 mg E_2 + 0.5 mg NETA (Activelle)
Number of women randomized	45	44	46
Age (years)	58.2 ± 4.3	58.0 ± 4.7	57.8 ± 4.6
Time since menopause (years)	9.3 ± 5.5	9.2 ± 6.4	8.4 ± 4.5
Body mass index (kg/m^2)	24.4 ± 3.2	24.8 ± 2.5	24.2 ± 3.1
BMD, lumbar spine (g/cm^2)	0.97 ± 0.11	1.01 ± 0.10	0.99 ± 0.09
Low bone mass, lumbar spine *(N)	12	4	9
Normal bone mass, lumbar spine **(N)	32	38	37

Data are presented as mean ± SD
** Low: low bone mass (t-score <-1 SD of the mean for healthy adult women)
*** Normal: normal bone mass (t-score >-1 SD of the mean for healthy adult women)
In the placebo and 1 mg E_2 + 0.25 mg NETA groups, the number of women with low and normal bone mass do not add up to the number of women randomized, as baseline BMD values were missing for 3 subjects.

Sponsor's Table. Age and Time Since Menopause

	KLIM/PD/11/USA		KLIM/PD/4/F	
	Placebo	Activelle	Placebo	Activelle
Age (years)	53.5 ± 3.5	52.5 ± 4.1	58.2 ± 4.3	57.8 ± 4.6
Time since menopause (years)	3.1 ± 1.3	3.1 ± 1.3	9.3 ± 5.5	8.4 ± 4.5

Data are presented as means ± SD

Efficacy

The primary efficacy, lumbosacral spinal BMD, and secondary efficacy, hip BMD, for the two studies are summarized in this section. From an efficacy perspective, this study was efficient, with a relatively small n but good statistical significance ($p<0.001$). The results of the other secondary efficacy outcome, change in biochemical markers of bone turnover, follow the BMD results.

Sponsor's Table. Mean Percentage Change in Bone Mineral Density (ITT with LOCF)

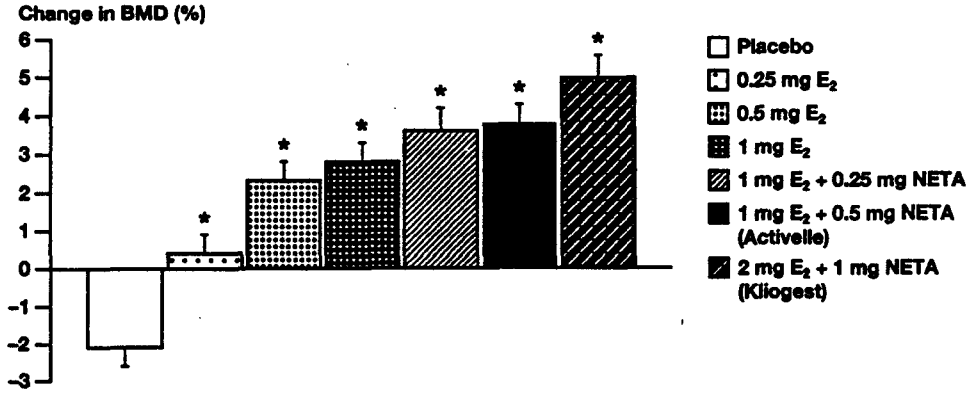
	KLIM/PD/11/USA		KLIM/PD/4/F	
	Placebo	Activelle	Placebo	Activelle
Lumbar spine	-2.1 ± 0.5	3.8 ± 0.5 *	-0.9 ± 0.6	5.4 ± 0.8 *
Femoral neck	-2.3 ± 0.6	1.8 ± 0.7 *	-1.0 ± 0.7	0.7 ± 0.9
Femoral trochanter	-2.0 ± 0.7	3.7 ± 0.7 *	0.8 ± 1.1	6.3 ± 1.2 *
Ward's triangle	-	-	-1.6 ± 1.3	2.7 ± 1.7
Distal radius	-	-	-0.7 ± 0.5	2.1 ± 0.5 *
Total body	-	-	0.4 ± 0.4	3.0 ± 0.5 *

* Significantly ($p<0.001$) different from placebo

Sponsor's Table. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (ITT with LOCF) - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
N	37	37	31	37	37	37	42
Mean ± SEM	-2.1 ± 0.5	0.4 ± 0.5*	2.3 ± 0.5*	2.8 ± 0.5*	3.5 ± 0.6*	3.8 ± 0.5*	5.0 ± 0.6*

n is the number of women contributing with data for the analysis
SEM: standard error of mean
* significantly ($p<0.001$) different from placebo



* Significantly ($p<0.001$) different from placebo

Sponsor's Figure. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (ITT with LOCF) - KLIM/PD/11/USA

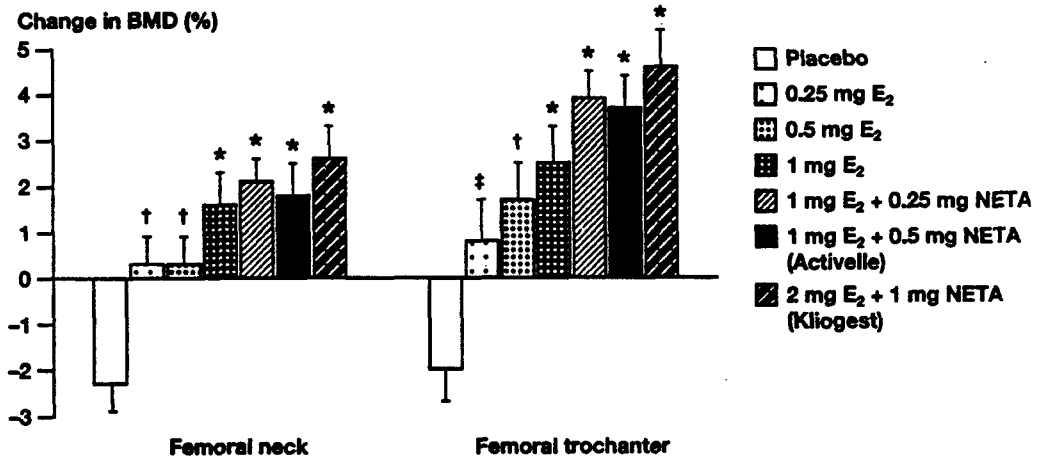
In terms of efficacy, all active treatments resulted in bone preservation at the lumbosacral spine. The study was designed to compare each treatment group to placebo but not to compare the

treatment groups to other treatment groups. From these data, it appears that a lower combination dose of E_2 and NETA may be effective in osteoporosis prevention.

Sponsor's Table. Mean Percentage Change in Bone Mineral Density at the Hip (ITT with LOCF) - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
n	37	37	30	36	37	37	42
Femoral neck Mean ± SEM	-2.3±0.6	0.3±0.6$	0.3±0.5$	1.6±0.7*	2.1±0.5*	1.8±0.7*	2.6±0.7*
Femoral trochanter Mean ± SEM	-2.0±0.7	0.8±0.9#	1.7±0.8$	2.5±0.8*	3.9±0.6*	3.7±0.7*	4.6±0.8*

n is the number of women contributing with data for the analysis
* significantly (p<0.001) different from placebo
$ significantly (p<0.01) different from placebo
# significantly (p<0.05) different from placebo



* Significantly (p<0.001) different from placebo
† Significantly (p<0.01) different from placebo
‡ Significantly (p<0.05) different from placebo

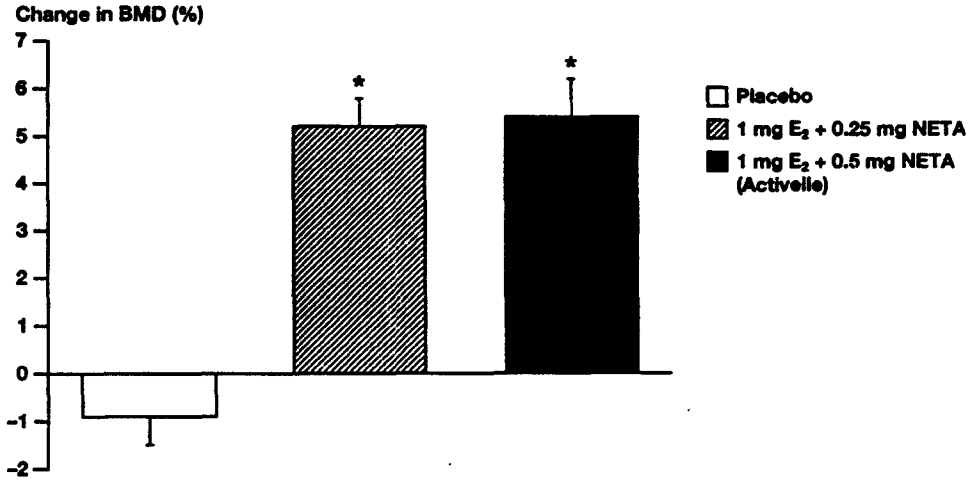
Figure 0-1 Mean Percentage Change in Bone Mineral Density at the Hip (ITT with LOCF) - KLIM/PD/11/USA

Similarly, all active treatment groups resulted in bone preservation at the hip as measured at the femoral neck and the femoral trochanter, with greater statistical significance (p<.001) for the higher dose estrogen and the combination estrogen progestin combinations (i.e., the treatment groups with greater estrogen exposure).

Sponsor's Table. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (ITT with LOCF) - KLIM/PD/4/F

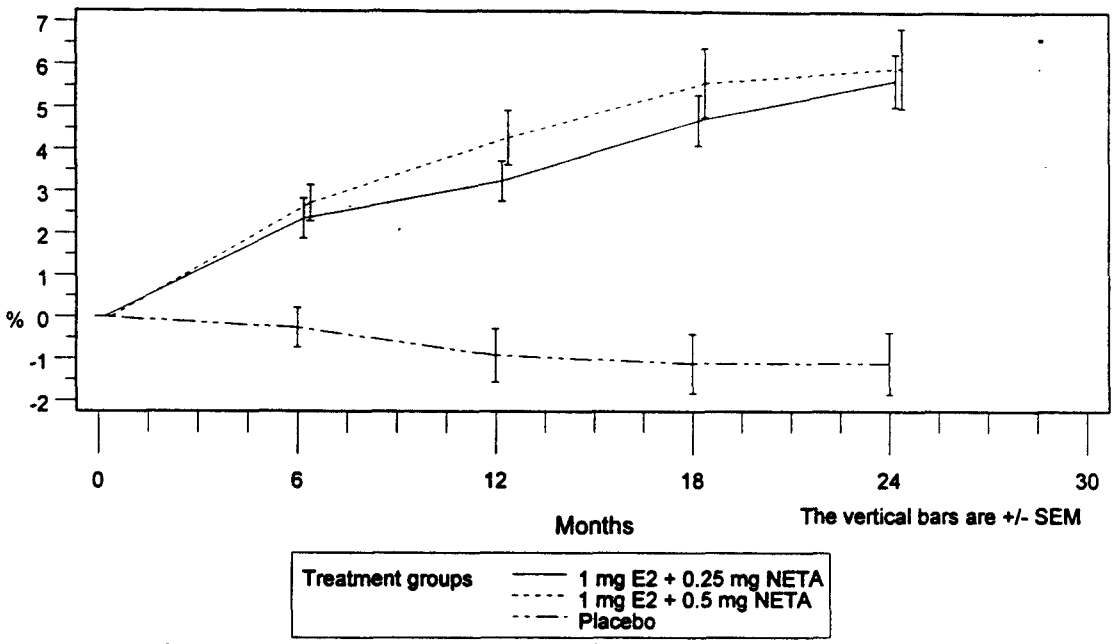
	Placebo		1 mg E_2 + 0.25 mg NETA		1 mg E_2 + 0.5 mg NETA (Activelle)	
Lumbar spine	n=40	-0.9% (0.6)	n=37	5.2% (0.6)*	n=38	5.4% (0.8)*

Data are provided as mean (standard error of mean)
n is the number of women contributing with data for the analysis
* significantly ($p<0.001$) different from placebo



* Significantly ($p<0.001$) different from placebo

Sponsor's Figure. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (ITT with LOCF) - KLIM/PD/4/F



Sponsor's Figure. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) over Time - KLIM/PD/4/F

As in KLIM/PD/11/USA, in KLIM/PD/4/F the efficacy of estrogen on osteoporosis prevention was more manifest in the spinal or vertebral bone, which is mostly trabecular, than in appendicular bones, which are more cortical.

Sponsor's Table. Mean Percentage Change in Bone Mineral Density at the Hip, Distal Radius, and Total Body (ITT with LOCF) - KLIM/PD/4/F

	Placebo		1 mg E_2 + 0.25 mg NETA		1 mg E_2 + 0.5 mg NETA (Activelle)	
Femoral neck	n=40	-1.0% (0.7)	n=36	1.5% (1.0)	n=38	0.7% (0.9)
Femoral trochanter	n=40	0.8% (1.1)	n=36	3.3% (1.0)	n=38	6.3% (1.2)*
Ward's triangle	n=40	-1.6% (1.3)	n=36	2.4% (1.6)	n=38	2.7% (1.7)
Distal radius	n=39	-0.7% (0.5)	n=36	0.9% (0.5)$	n=36	2.1% (0.5)*
Total body	n=39	0.4% (0.4)	n=36	2.5% (0.5)*	n=38	3.0% (0.5)*

Data are provided as mean (standard error of mean)
n is the number of women contributing with data for the analysis
* significantly ($p<0.001$) different from placebo
$ significantly ($p<0.01$) different from placebo

Interestingly, the smaller and shorter (6-month) Japanese study also showed significant efficacy in lumbosacral BMD preservation.

Sponsor'sTable. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_2-L_4) (LOCF) - KLIM/PD/18/J

	Placebo		1 mg E_2 + 0.5 mg NETA (Activelle)		2 mg E_2 + 1 mg NETA	
Efficacy population	n=9	-0.5% (1.4)	n=8	4.8% (1.0)$	n=6	7.3% (1.6)$
ITT population	n=14	-1.8% (1.2)	n=13	3.8% (0.8)$	n=12	7.8% (1.3)$

Data are provided as mean (standard error of mean)
n is the number of women contributing with data for the analysis
$ significantly (p<0.01) different from placebo

Treatment with estrogen and the estrogen-progestin combinations resulted in a decrease in bone resorption markers and to a lesser extent decrease in bone formation markers, as indicated below.

Sponsor's Table. Percentage Change in Biochemical Markers of Bone Turnover - Adequate and Well-controlled Trials

	KLIM/PD/11/USA		KLIM/PD/4/F	
	Placebo	Activelle	Placebo	Activelle
Resorption				
U-CTX	-	-	-6%	-60% *
U-pyridinoline	-6%	-17% *	-	-
U-deoxypyridinoline	-9%	-34% *	-	-
Formation				
serum osteocalcin	-	-	-3%	-34% *
serum bone-specific alkaline phosphatase	114%	42% *	2%	-29% *
serum C-terminal propeptide of type I collagen	-	-	-1%	-19% *

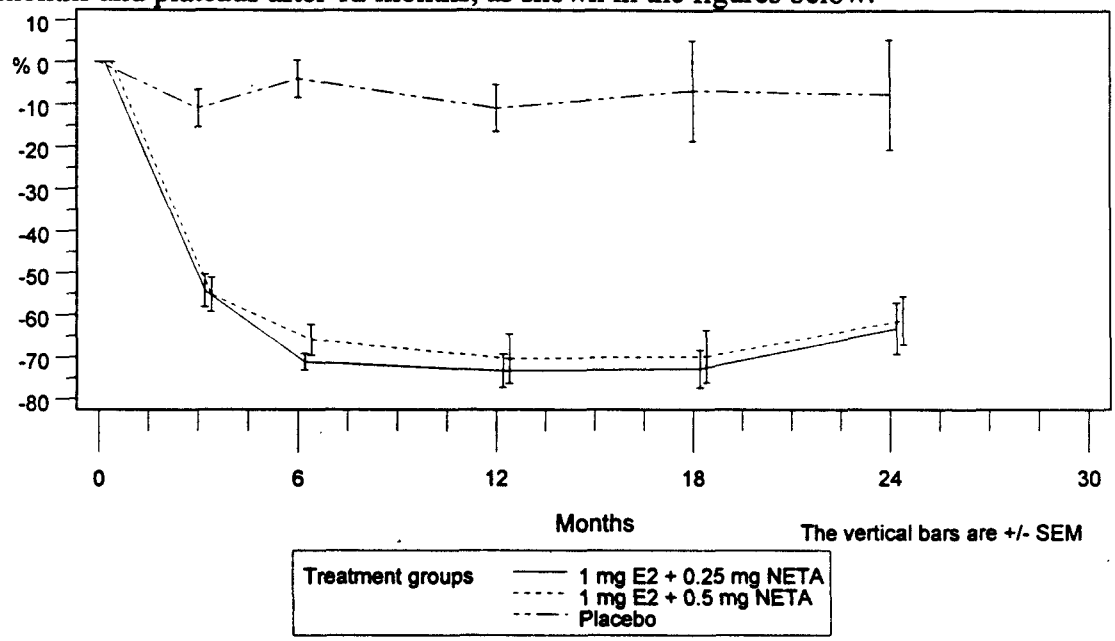
Data from KLIM/PD/11/USA are median percentage change.
Data from KLIM/PD/4/F are mean percentage change
u-CTX: urinary pyridinoline crosslinks Type I collagen C-telopeptide
* Significantly (p<0.05) different from placebo

Sponsor's Table. Median Percentage Change in Biochemical Markers of Bone Turnover (ITT with LOCF) - KLIM/PD/11/USA

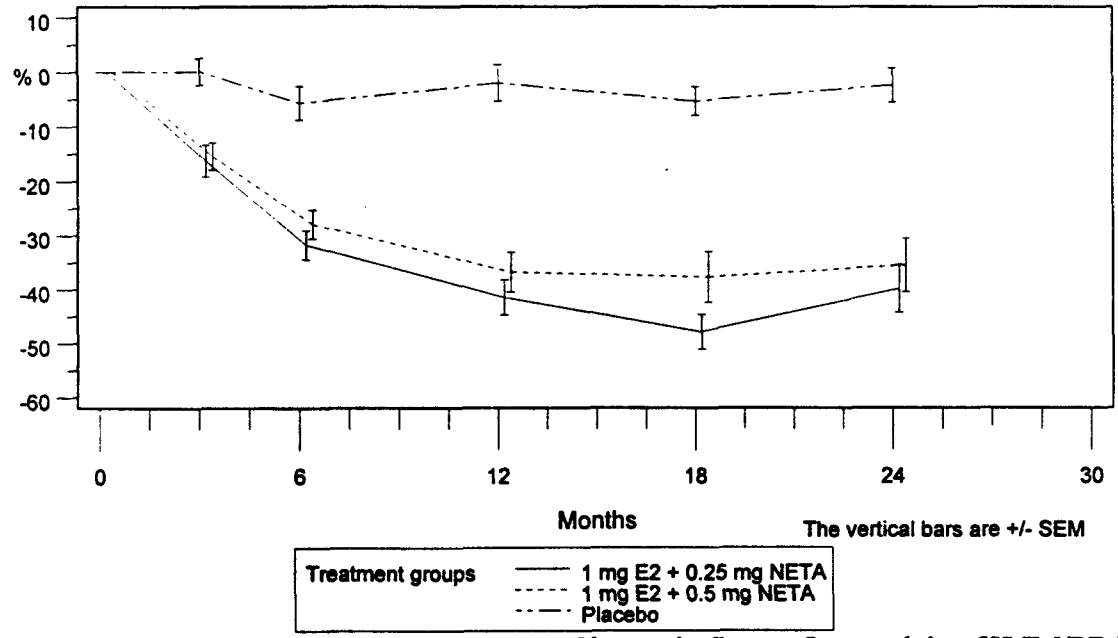
		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
Urinary pyridinoline							
Median	-6	-16	-22	-22	-28 *	-17 *	-23
Min; max							
Urinary deoxypyridinoline							
Median	-9	-28 *	-22 *	-28 *	-42 *	-34 *	-36 *
Min; max							
BSAP							
Median	114	66	90	74 *	42 *	42 *	8 *
Min; max							

BSAP: bone-specific alkaline phosphatase
* significantly (p<0.05) different from placebo

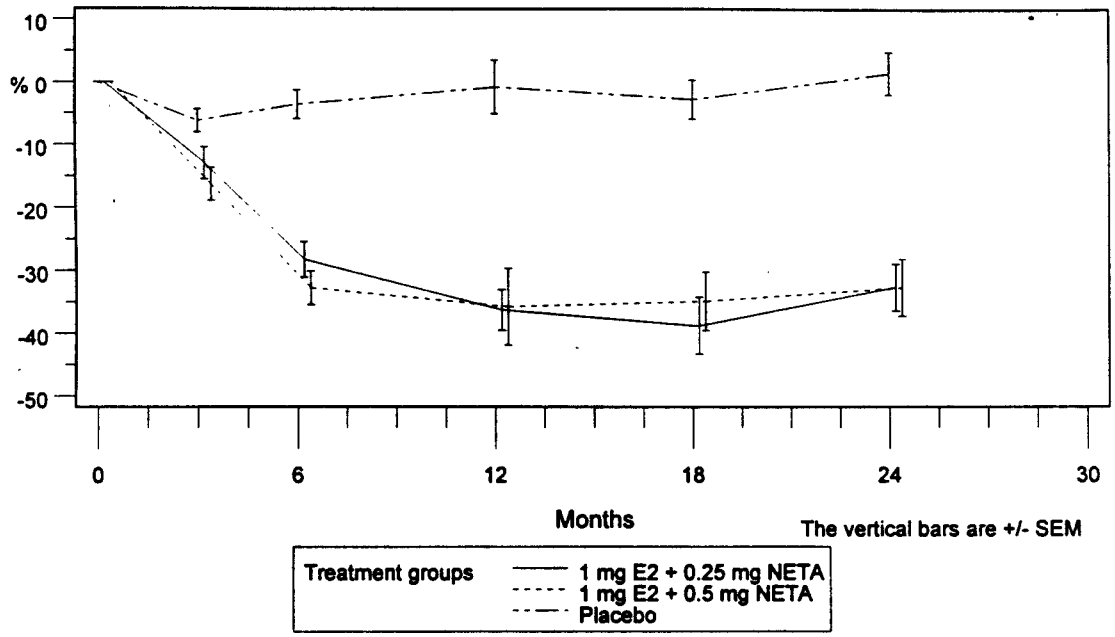
The time course of change in biochemical markers of bone turnover is primarily in the first 6-12 months and plateaus after 12 months, as shown in the figures below.



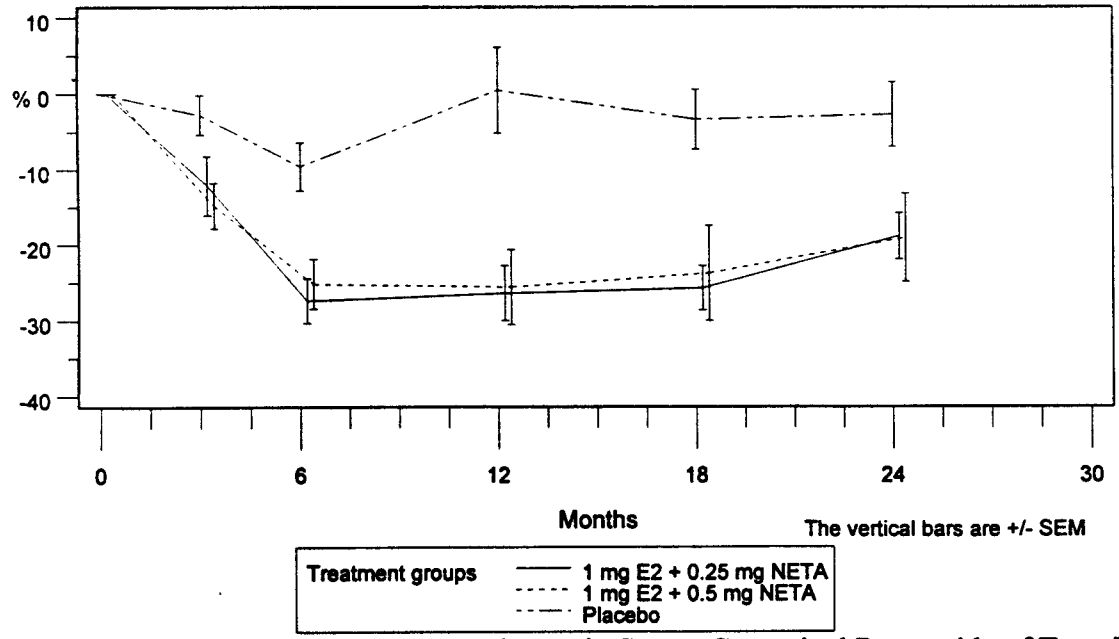
Sponsor's Figure. Mean Percentage Change in Urinary Pyridinoline Crosslinks Type I Collagen C-telopeptide - KLIM/PD/4/F



Sponsor's Figure. Mean Percentage Change in Serum Osteocalcin - KLIM/PD/4/F



Sponsor's Figure. Mean Percentage Change in Serum Bone-specific Alkaline Phosphatase - KLIM/PD/4/F



Sponsor's Figure. Mean Percentage Change in Serum C-terminal Propeptide of Type I Collagen - KLIM/PD/4/F

Again, similar trends in decreased bone turnover, with decreased bone formation and bone resorption markers, are seen in the 6-month Japanese study.

Sponsor's Table. Mean Percentage Change in Biochemical Markers of Bone Turnover (LOCF) - KLIM/PD/18/J

	Placebo			1 mg E_2 + 0.5 mg NETA (Activelle)			2 mg E_2 + 1 mg NETA		
U-CTX									
Efficacy population	n=8	43%	(51)	n=8	-68%	(7) #	n=6	-84%	(2) #
ITT population	n=15	42%	(40)	n=15	-28%	(41)#	n=13	-80%	(4) #
BSAP									
Efficacy population	n=8	28%	(17)	n=8	-17%	(9) #	n=6	-28%	(8) #
ITT population	n=15	12%	(10)	n=15	-4%	(16)#	n=13	-16%	(12)#

Data are provided as mean (standard error of mean)
n is the number of women contributing with data for the analysis
U-CTX: urinary pyridinoline crosslinks Type I collagen C-telopeptide
BSAP: bone-specific alkaline phosphatase
significantly ($p<0.05$) different from placebo

Sponsor's Comments Regarding Long Term Effectiveness, Tolerance, and Withdrawal Symptoms

Clinical trials assessing the changes of bone mineral density and biochemical markers of bone turnover after 2 years of treatment have been performed to document the efficacy of the 1 mg E_2 + 0.5 mg combination NETA (Activelle). The effect of therapy was evaluated in clinical trials of up to 2 years duration. After 2 years, an overall difference in lumbar spine BMD between Activelle and placebo-treated women of approximately 6% was found in the adequate and well-controlled trials. Activelle was also associated with increases in BMD at other skeletal sites. No clinical trials beyond 2 years duration have been performed with Activelle on bone mineral density or biochemical markers of bone turnover. Based on published reports with higher dose combinations with E_2 and NETA, the increase in BMD achieved with Activelle at various skeletal sites over the initial 2 years treatment is expected to be at least maintained during continuous therapy with Activelle.

The trials presented in this ISE documented that Activelle normalizes bone turnover in postmenopausal women. The changes in biochemical markers of bone turnover associated with Activelle were marked during the initial 3-6 months (for resorption markers) or 6-12 months (for formation markers) of therapy, with almost no change in bone markers during the second year of treatment. No clinical trials beyond 2 years duration have been performed with Activelle on biochemical markers of bone turnover; however, based on the flat profile in bone markers observed during the second year of treatment with Activelle, no major changes in the levels of bone markers would be expected with continuous therapy with Activelle.

The effect on bone loss after discontinuation of Activelle treatment has not been investigated in clinical trials. Published data on the effects of discontinuation with higher dose combinations of E_2 and NETA have indicated that the annual rate of bone loss is identical to that in the placebo group. Discontinuation of HRT has not been associated with an excess loss (catch-up loss) and the amount of bone saved during estrogen therapy appears to be preserved for at least 7 years after discontinuation of treatment.

Concerning the fracture risk, epidemiological data have suggested that hormone replacement therapy decreases the risk of vertebral fracture by about 50% and the risk of hip fracture by about 25%. The fracture prevention effect of hormone replacement therapy has been suggested to be greater in long-term users. The protective effect on fractures appear to be lost within few years after treatment discontinuation.

Finally, no withdrawal symptoms in the general understanding of withdrawal symptoms are expected following discontinuation of Activelle treatment. Recurrence of menopausal symptoms in women who had symptoms present at initiation of therapy would be expected to some degree. No information is available on the presence of bleeding following withdrawal of Activelle treatment.

Sponsor's Conclusions

From the results and analyses of the two adequate and well-controlled trials, the following can be concluded:

- Treatment with 1 mg E_2 in combination with 0.5 mg NETA (Activelle) increases bone mineral density at the lumbar spine. The difference in bone mineral density change at the lumbar spine between active treatment and placebo is approximately 6% after 2 years of treatment.

- Activelle (1 mg E_2 + 0.5 mg NETA) was effective in preventing bone loss at several skeletal sites, including the lumbar spine, hip, distal radius, and the total body in postmenopausal women. Activelle (1 mg E_2 + 0.5 mg NETA) was effective in preventing bone loss in early postmenopausal women. Most women maintained or gained bone mineral density at the lumbar spine during treatment with Activelle.

- Treatment with Activelle (1 mg E_2 + 0.5 mg NETA) normalised bone turnover, shown by a marked decrease in bone resorption markers and to a lesser extent in bone formation markers.

Clinical Safety

Deaths and Protocol Violations

Deaths
[Summarized per Medical Officer]

(IPS=International Product Safety Number)

IPS Number	Study	Age	Drug	Duration	Cause of Death
105802	11/USA	58	E2 1 mg NETA 0.5 mg	11/1/95 – 3/3/97 (493 d)	Metastatic cancer, primary unknown, ovarian cancer on death certificate, no autopsy; history of malignant breast neoplasm
100474	4/F	58	E2 1 mg NETA 0.5 mg	4 months	Myocardial infarction (history of coronary artery disease)
105178	4/F	65	Placebo	3/21/96- 1/11/97	Found dead at home ? cardiac arrest or internal hemorrhage (treated with anticoagulant for arrhythmia)
105678	19/USA	54	E2 1 mg NETA 0.5 mg	10/3/96 – 2/5/97	Lung cancer (history cigarette smoking)

The deaths occurred in the longer studies (KLIM/PD/11/USA and KLIM/PD/4/F were two-year studies; KLIM/PD/19/USA was a one-year study). Three of the four deaths occurred in subjects who had been randomized to E2 1 mg NETA 0.5 mg. The two deaths in KLIM/PD/4/F occurred in subjects who did not meet the study inclusion/exclusion criteria: history of coronary artery disease and arrhythmia were exclusion criteria. The death in KLIM/PD/11/USA also had a possible protocol violation – prior history of malignant breast neoplasm.

Even though the 4 deaths represent only 0.5 % (4/817) of the randomized population of the five studies submitted in this NDA or 0.6 % (3/462) of the population randomized to the two two-year osteoporosis studies, the deaths in women on study drug who did not meet initial

inclusion/exclusion criteria raise a signal or suggestion of possible events that may occur when women less healthy than the selected population in these clinical trials are exposed to E_2 NETA. These protocol violations raise question about the integrity of the study and particularly the attention to inclusion/exclusion criteria for the other 813 randomized subjects. Of note, none of these protocol deviations were listed in the sponsor's list of protocol deviations.

Two other protocol violations have been noted in the review of the serious adverse events. One subject in KLIM/PD/11/USA developed back pain, a Tarlov's cyst L5-S1, and right-sided sciatica on day 493 of E_2 1 mg NETA 0.5 mg and had a medical history of osteoporosis. Another subject (5/429) on KLIM/PD/11/USA treated with E_2 1 mg NETA 0.5 mg was diagnosed with asthma on day 168 and continued on trial with prednisone therapy. The change in spinal BMD for subject 429 was 2.4 and 4.7% at 13 and 19 months, respectively. (No data at 26 months was available.) These protocol violations represent approximately 1% (4/462) of the population randomized to the two-year studies of osteoporosis.

Discontinuation Secondary to Adverse Events From KLIM/PD/11/USA
(Table per Medical Officer)

Treatment Group	Placebo	E_2 0.25 mg	E_2 0.5 mg	E_2 1 mg	E_2 1 mg NETA .25mg	E_2 1 mg NETA .5mg	E_2 2 mg NETA 1mg
# Randomized	48	45	44	46	49	47	48
Total # (%) Adverse Event Discontinuations	11 (23%)	9 (20%)	6 (14%)	16 (35%)	7 (14%)	8 (17%)	8 (17%)
Postmenopausal bleeding			2	6	2	3 (6 %)	5
Breast pain	2 (4%)			1	1	3 (6 %)	2
Endometrial hyperplasia	1	1	1	5			
Hot flushes	4		1		1		
Weight gain		2	1				
Abdominal Pain		2	1	1		1	2
Depression/ anxiety/ nervousness/ emotional lability	1			2	1	2	
headache				1			
Prolapsed uterus			1 (361 days)				
Back pain/ Tarlov's cyst L5-S1 Right sciatica (Hx. Osteoporosis)							1 (527 days)
Breast neoplasm		1 (495 days)					
Ovarian neoplasm (endometrioma)					1 (365 days)		
Metastatic Adenocarcinoma						1	

(?ovarian) (hx. Malignant neoplasm of breast)						(493 days) (died 2 months later)	

Discontinuation Secondary to Adverse Events From KLIM/PD/4/F (Table per Medical Officer)			
Treatment Group	Placebo	E2 1 mg NETA 0.25 mg	E2 1 mg NETA 0.5 mg
# Randomized	45	44	46
Total # (%) Adverse Event Discontinuations	6 (13%)	11 (25%)	13 (28%)
Postmenopausal bleeding		2	2 (4%)
Breast pain		2	5 (11%)
Endometrial hyperplasia*			
Vertebral Fractures	2		
Phlebitis		3	
Headache			3
Hypertension		1	
Myocardial Infarct			1 (death)
asthenia			1
Breast neoplasm/ Fibroadenosis**			2
Cervical uterine polyp			1
Hepatic cancer			1
*Bleeding was assessed by daily logs, but no endometrial biopsies were included in the protocol. **The breast neoplasm was benign; the subject with fibroadenosis was lost to followup.			

Thus, breast pain and postmenopausal bleeding were adverse events that resulted in 6 to 11 % and 4 to 6% of the subject withdrawals in KLIM/PD/11/USA and KLIM/PD/4/F, respectively. Reasons for discontinuation of E_2 1 mg NETA .25 mg and E_2 1 mg NETA .5 mg in KLIM/PD/19/USA and E_2 1 mg NETA .5 mg in KLIM/PD/15/IRL also included postmenopausal bleeding, dizziness/sluggishness/agitation/ bloating, pelvic pain, and breast pain. Similarly, there was a high prevalence of treatment-emergent breast pain and postmenopausal bleeding among the women treated with the combination estrogen-progestin in these two trials. The prevalence of these reproduction –related adverse events in the E_2NETA treatment groups was significantly greater than in the placebo group or lower dose estrogen alone groups, as shown in the table below. (The full summary of 5% treatment-emergent adverse events is listed in the Appendix.) The only other category in KLIM/PD/11/USA with a higher prevalence of adverse events in E_2/NETA was "injury accidental."

Treatment-emergent Adverse Events Reported by ≥5% of Women in a Treatment Group - KLIM/PD/11/USA

	Unopposed E_2 (mg)				E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1+0.25	1+0.5 Activelle	2+1
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Women randomised	48	45	44	46	49	47	48
Adverse events	41(85)	39(87)	36(82)	40(87)	40(82)	39(83)	45(94)
REPRODUCTION DISORDERS							
Breast pain female	4(8)	1(2)	2(5)	4(9)	5(10)	8(17)	6(13)
Postmenopausal bleeding	0	1(2)	3(7)	9(20)	3(6)	5(11)	6(13)
Breast disorder nos	1(2)	0	1(2)	3(7)	1(2)	0	1(2)
Endometrial disorder	3(6)	2(4)	4(9)	12(26)	1(2)	0	4(8)
Endometrial hyperplasia	1(2)	1(2)	1(2)	6(13)	0	0	0
SECONDARY TERMS							
Injury accidental	2(4)	2(4)	1(2)	6(13)	7(14)	8(17)	4(8)

Table -4 Treatment-emergent Adverse Events Reported by ≥5% of Women in a Treatment Group - KLIM/PD/4/F

System Organ Class	Placebo			1 mg E_2 +0.25 mg NETA			1 mg E_2 +0.5 mg NETA Activelle		
(WHO)	N	(%)	E	N	(%)	E	N	(%)	E
REPRODUCTIVE DISORDERS, FEMALE									
Breast pain female	4	(9%)	4	17	(39%)	20	16	(35%)	18
Postmenopausal bleeding	3	(7%)	3	13	(30%)	17	6	(11%)	9
Vaginitis	1	(2%)	1	3	(7%)	4	4	(9%)	4
Leukorrhoea	0			2	(5%)	2	1	(2%)	1
Vaginal haemorrhage *	0			1	(2%)	1	1	(2%)	1

N = number of subjects
% = proportion of exposed subjects having the event
E = number of adverse events
* = vaginal haemorrhage is included as it will be presented with postmenopausal bleeding

Also, depression and emotional lability and thrombophlebitis were more prevalent as treatment emergent adverse events in the E_2NETA treatment groups.

Reviewer's Comments:

The most important observations about the adverse events in the safety data are the following:

1) the data set of the safety studies represents a relatively small population of women exposed to the combination doses of E_2NETA exposed for two years, while the target population is large and may be exposed to the drug for a longer period, particularly for the osteoporosis indication;
2) the study patient populations were healthy and relatively newly postmenopausal with a multitude of inclusion and exclusion criteria; the target population may be older and have more chronic diseases;
3) in other words, the study population may not be representative of the target population, and more adverse events may be expected in the target population;
4) whereas women may be willing to tolerate more adverse events for a shorter-term indication, such as relief of hot flushes, paucity of adverse events is important in maintaining compliance with a long-term regimen;
5) breast pain and postmenopausal bleeding will decrease the compliance with the regimen;

6) since bleeding is unusual in the postmenopausal population, persistent bleeding will result in anxiety, extra interventions such as medical visits and procedures, and potentially significant additional health care costs.

Breast Cancer

There are three cases of breast cancer reported in this NDA: Two cases in KLIM/PD/11/USA (E_2 .25 mg and E_2 1 mg) and one case in 19/USA (placebo). In addition, Dr. Price reported seven cases of malignant breast neoplasm distributed among the treatment groups in KLIM/PD/7/USA. The reviewer agrees with the sponsor that the sample size is too small to draw any conclusions form the breast cancer data or even the mammography data from KLIM/PD/11/USA.

Endometrial and Cervical Effects

Sponsor's Table. Endometrial Histology at the End of the Trial- KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
Randomized	48	45	44	46	49	47	48
Histol. eval.	35	32	30	32	33	35	41
Normal							
Insuff. tissue	15 (43%)	11 (34%)	5 (17%)	3 (9%)	7 (21%)	10 (29%)	8 (20%)
Atrophic	19 (54%)	20 (63%)	22 (73%)	10 (31%)	24 (73%)	22 (63%)	28 (68%)
Proliferative	0	1 (3%)	2 (7%)	10 (31%)	2 (6%)	3 (9%)	3 (7%)
Other	0	0	0	0	0	0	1 (3%)*
Abnormal							
Simple hyperp.	0	0	1 (3%)	8 (25%)	0	0	0
Complex hyperp.	1 (3%)	0	0	1 (3%)	0	0	0
Disord. prolif.	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	1 (3%)*

* The endometrial slides were evaluated by a pathologist local to the trial center and classified as Normal Other and Abnormal Other, respectively. The slides were subsequently lost and no 2nd or 3rd readings could be performed.

Although there were no cases of hyperplasia, there was a tendency to a higher percentage of proliferative changes in the E_2 1 mg NETA .05 mg treatment group. The addition of progestin did prevent significant endometrial thickening, as assessed by vaginal ultrasound.

Sponsor's Table. Endometrial Thickness - KLIM/PD/11/USA-

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
Randomized	48	45	44	46	49	47	48
Baseline							
Mean ± SD (mm)	3.0±1.2	3.1±1.2	2.7±1.2	3.3±1.3	3.2±1.3	2.9±1.0	3.3±1.3
Median (mm)	3.0	3.0	3.0	3.0	3.5	3.0	3.0
End-of-trial							
Mean ± SD (mm)	3.3±1.8	4.3±2.8	4.5±2.2	6.9±4.7	3.9±1.8	3.6±1.9	4.7±3.2
Median (mm)	3.0	3.6	4.0	5.7	4.0	3.1	4.0
Change from baseline							
Mean ± SD (mm)	0.2±2.0	1.3±2.7	1.9±2.3	3.5±4.9	0.7±1.6	0.6±1.7	1.4±3.2
Median (mm)	0.0	0.9	1.6	2.5	0.2	0.5	1.0

Sponsor's Table. Proportion of Women Bleeding/Spotting - KLIM/PD/4/F

	Placebo	1 mg E_2 +0.25 mg NETA	1 mg E_2 +0.5 mg NETA (Activelle)
Number of Women	45	44	46
Cycle 1 - 6			
No at risk	39	38	41
No bleeding/spotting	4 (10.3 %)	15 (39.5 %)	15 (36.6 %)
Cycle 7 - 12			
No at risk	33	31	30
No bleeding/spotting	0 (0.0 %)	10 (32.3 %)	5 (16.7 %)
Cycle 13 - 18			
No at risk	31	26	27
No bleeding/spotting	1 (3.2 %)	4 (15.4 %)	2 (7.4 %)
Cycle 19 - 24			
No at risk	28	24	26
No bleeding/spotting	1 (3.6 %)	6 (25.0 %)	2 (7.7 %)

No at risk: Number of women randomised who were not hysterectomised
No bleeding/spotting: Number of women who experienced bleeding or spotting at least once during a six months period of time.

A significant number of women continued to bleed at the end of two years (25 % for E_2 1mg NETA .25 mg and 8% for E_2 1mg NETA .5 mg.), and an even greater percentage were bleeding at 6 months (as noted in the tables above and below [KLIM/PD/18/J is 6-month study]).

Sponsor's Table. Proportion of Women Bleeding/Spotting - KLIM/PD/18/J

	Placebo	1 mg E_2 + 0.5 mg NETA (Activelle)	2 mg E_2 + 1 mg NETA
Women exposed	16	16	15
Non-hysterectomised women	12	11	10
Bleeding/Spotting	0	4 (36.4 %)	6 (60.0 %)

Sponsor's Table. Papanicolaou Smear at the End of the Trial - KLIM/PD/19/USA

	Placebo (N=68) N (%)	1 mg E_2 (N=67) N (%)	1 mg E_2 + 0.25 mg NETA (N=68) N (%)	1 mg E_2 + 0.5 mg NETA (Activelle) (N=67) N (%)
Women with Pap result	63	63	60	61
I	60 (95.2)	60 (95.2)	54 (90.0)	58 (95.1)
IIa	2 (3.2)	2 (3.2)	4 (6.7)	2 (3.3)
IIb	1 (1.6(	1 (1.6(	2 (3.3)	1 (1.6)
III-CIN1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
III-CIN2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IV-CIN3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CIN: cervical intraepithelial neoplasia.
For definitions, please refer to Maguire NC, Diagn Cytopathol 1988; 4: 169-176.

Sponsor's Table. Vaginal Cytology, Maturation Value - KLIM/PD/19/USA

	Placebo (N=68)	1 mg E_2 (N=67)	1 mg E_2 + 0.25 mg NETA (N=68)	1 mg E_2 + 0.5 mg NETA (Activelle) (N=67)
Baseline				
Smears obtained, N	67	67	66	66
Smears readable, N (%)	41 (61.2%)	40 (59.7%)	27 (40.9%)	43 (65.2%)
Mean (SD)	46.5 (13.5)	48.1 (11.9)	48.0 (8.4)	42.2 (13.6)
End-of-trial				
Smears obtained, N	62	64	63	57
Smears readable, N (%)	37 (59.7%)	60 (93.8%)	62 (98.4)	51 (89.5%)
Mean (SD)	45.6 (14.5)	66.2 (11.2)	68.6 (14.6)	63.1 (12.0)
Baseline to end-of-trial				
Smears included, N	27	34	24	33
Mean (SD)	-0.7 (14.7)	19.2 (18.6)	19.2 (11.9)	19.0 (20.2)

Maturation value = 0.5*(intermediate cells) + (superficial cells)

Lipid Changes

Although an increase in total cholesterol is noted with E_2NETA therapy, there is a favorable decrease in LDL concentration in comparison to placebo and a favorable decrease in triglyceride concentration when compared to estrogen.

Sponsor's Table. Mean Percentage Change from Baseline to the End of the Trial in Lipids and Lipoproteins - KLIM/PD/19/USA

	Placebo (N=68)	1 mg E_2 (N=67)	1 mg E_2 + 0.25 mg NETA (N=68)	1 mg E_2 + 0.5 mg NETA (Activelle) (N=67)
Total cholesterol	-1%	3%	6% *	10% * #
LDL-cholesterol	-3%	-11% *	-11% *	-14% *
HDL-cholesterol	8%	13%	5% #	1% * #
Triglycerides	-1%	19% *	4%	-7% #
Apo A-1	-2%	8% *	-2% #	-5% #
Apo B	-2%	-2%	-6%	-8% * #

* significantly ($p<0.05$) different from placebo
# significantly ($p<0.05$) different from 1 mg E_2

Sponsor's Table . Mean Percentage Change from Baseline to the End of the Trial in Lipids and Lipoproteins - KLIM/PD/15/IRL

	1 mg E_2	1 mg E_2 + 0.5 mg NETA (Activelle)
Total cholesterol	-9.6% ϕ	-8.6% ϕ
LDL-cholesterol	-17.5% ϕ	-17.0% ϕ
HDL-cholesterol	3.6%	3.1%
VLDL-cholesterol	10.6%	4.7%
Triglycerides	1.0%	5.9%
Lipoprotein (a)	-1.5%	-28.9% ϕ

ϕ significantly ($p<0.05$) different from baseline

Esradiol Concentrations

Estradiol concentrations increased with increasing dosage of estrogen replacement. In KLIM/PD/11/USA, estradiol concentrations increased from < 10 pg/ml to an end of trial median of approximately 60 pg/ml in both E2NETA groups.

Sponsor's Table. Estradiol Levels - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5	2 + 1
Estradiol (pg/ml)							
Baseline, median	7.0	9.0	9.0	8.0	9.0	6.0	8.5
End-of-trial, median	9.0	24.0	39.5	62.0	60.0	58.5	91.5

1 mg E_2 + 0.5 mg NETA: Activelle

In KLIM/PD/4/F, estradiol concentrations increased from a baseline mean of < 15 pg/ml to approximately 40 pg/ml for the E_2NETA groups. It is unclear if the difference in concentrations

between the two studies reflects the different populations and/or different analytic methodologies.

Sponsor's Table. Estradiol and FSH Levels - KLIM/PD/4/F

	Placebo	1 mg E_2 + 0.25 mg NETA	1 mg E_2 + 0.5 mg NETA (Activelle)
Estradiol (pg/ml)			
Baseline, median	15.0	13.5	13.0
End-of-trial, median	12.0	36.0	40.0
FSH (IU/L)			
Baseline, median	71.0	70.0	73.8
End-of-trial, median	82.4	54.8	51.0

Glucose and Insulin Concentrations

Glucose and insulin concentrations did not increase in comparison to placebo or baseline E_2 NETA measurements; there appeared to be a slight decrease in glucose and insulin concentrations in the E_2NETA treatment group.

Blood Pressure, Weight, and Height

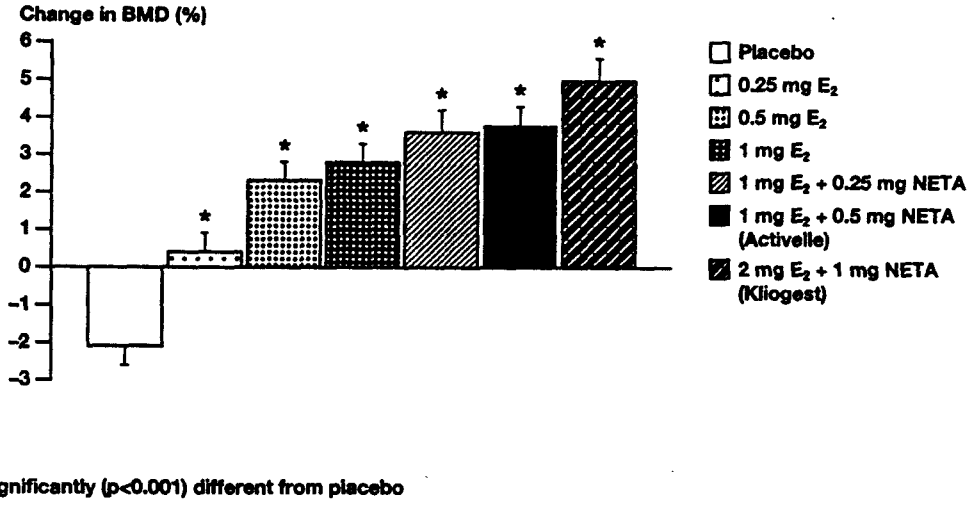
No significant changes in blood pressure was seen among the treatment groups. In KLIM/PD/11/USA, there were no significant weight changes, but in KLIM/PD/4/F a 2 % weight gain was noted in the E2 1 mg NETA 0.5 mg treatment group (versus –0.7 % in E2 1 mg NETA 0.25 mg and 0.4 % in placebo). No change in height was reported for either osteoporosis study. In the SAS data set for KLIM/PD/11/USA, the same height and the same weight were reported for all visits for a given subject. Either the measurements were not repeated at subsequent study visits or there was a data entry error.

Fracture

Neither of the two osteoporosis studies had fracture as an endpoint. In KLIM/PD/4/F, three subjects with fractures (2 vertebral and 1 humerus) were reported as serious adverse events in the placebo group, and none were reported in the active treatment groups.

11 Overview of Efficacy and Safety Conclusions

The sponsor concludes that all active treatment groups significantly increase the BMD of the spine and proximal femur in the two two-year osteoporosis studies (KLIM/PD/11/USA and KLIM/PD/4/F), as shown in the sponsor's figure below (also duplicated in the Results section).



Sponsor's Figure. Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (ITT with LOCF) - KLIM/PD/11/USA

However, the sponsor does not indicate the reasons for the selection of E_2 1mg NETA 0.5 mg for marketing for the indication of prevention of osteoporosis other than as a business decision that only one combination of E_2NETA would be marketed in the US. E_2 1 mg NETA 0.5 mg was the best studied dose for the prevention of postmenopausal symptoms, but it does not appear to be the best dose for osteoporosis prevention. Based on the effect on lumbosacral BMD in KLIM/PD/11/USA of the different strengths of E_2 and combination E_2NETA studied, it appears that a combination of a lower E_2 and possibly also lower NETA (e.g., E_2 0.5 mg NETA 0.5 mg, E_2 0.25 mg NETA 0.5 mg, E_2 0. 5 mg NETA 0.25 mg or E_2 0.25 mg NETA 0.25 mg). Of note, a small amount of NETA is metabolized to EE, so that administration of NETA 0.5 mg equals approximately 1.4 mcg EE. Exposure to an effectively lower chronic estrogen dose would also minimize the significant number of estrogen-related adverse events (e.g., postmenopausal bleeding and breast pain) and improve long-term compliance with chronic therapy.

The minimum effective dose of estrogen and progestin is emphasized in the the Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women, published in 1995 *after* these studies were initiated: "Approvals of specific fixed dose estrogen/progestin HRT products for estrogen class labeling indications will be based on the combination drug policy (see 21 CFR 300.50) and the determination, within reasonable limits, that a combination drug contains the lowest effective dosages of each of its active components for their respective labeled indications." Thus, the label must include the comment: "The doses of 17β - estradiol and

norethindrone acetate in Activella may not be the lowest effective dose-combination for prevention of osteoporosis."

In addition, the sponsor should be requested – or at the very least, encouraged - to conduct a rigorous dose-ranging post-marketing two-year osteoporosis study to identify the lowest effective combination dose and include an ineffective combination dose. Of note, no ineffective combination dose was studied in the clinical trials in this NDA. A one-year interim analysis would be important to evaluate which dosage is most effective with the relatively best safety profile. Since the population that takes estrogen progestin products for the prevention of osteoporosis is often older than the population studied in the osteoporosis clinical trials and since the elderly may be even more sensitive to these products because of changes in metabolism and excretion, the sponsor should be encouraged to also include older postmenopausal women in the suggested dose-ranging two-year osteoporosis prevention study.

12 General Comments

Comparison of 17β–estradiol norethindrone acetate (E_2NETA) **and ethinyl estradiol norethindrone acetate** (EENETA)

The approximately equivalent parenteral dosages of estrogens are estradiol 50 μg (E_2), ethinyl estradiol 50 μg (EE), and conjugated estrogens 5mg (Goodman and Gilman's Pharmacological Basis of Therapeutics, 7th ed., 1985). Diminished efficacy of oral agents such as estradiol is cited, but no equivalence is described for the oral preparations. Estradiol (micronized) tablets are listed as 1- and 2-mg tablets and ethinyl estradiol as 0.02 to 0.5 mg.

Although there are no published clinical trials comparing E_2NETA and EENETA for the prevention of osteoporosis, and E_2NETA and EENETA were studied separately for this indication, there are significant safety differences noted in the two-year clinical trials for these drugs.

Comparison of E_2NETA and EENETA

(Table is a summary of NDA 21103 and NDA 21102, by medical officer.)

		E_2NETA (Activelle) * (1994-8)		EENETA (femhrt) ** (1989-93)		
		Placebo	E_2 1 mg NETA.5 mg	Placebo	EE 5 mcg NETA 1 mg	EE 10 mcg NETA 1mg
N randomized	Total	93	93	137	146	145
	11/USA	48	47			
	4/F	45	46			
N ITT (LOCF)	11/USA	37	37	123	124	118
	4/F	40	38			
N completed	11/USA	28	24	97	102	98
	4/F	33	29			
Age	11/USA	53.5	52.5	52	52	52
	4/F	58.2	57.8			
Time since Menopause	11/USA	3.1 yrs	3.1 yrs	31 mths	30 mths	29 mths
	4/F	9.3 yrs	8.4 yrs			
Daily Calcium Supplementation	11/USA	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg
	4/F	500 mg	500 mg			
Lumbosacral spinal BMD (baseline) (SD) - E_2NETA (SE) - EENETA	11/USA	1.09 (.15) g/cm^2	1.11 (.15) g/cm^2	119.5 (2.0) mg/cc	117.8 (1.6) mg/cc	119.4 (1.9) mg/cc
	4/F	0.97 (.11) g/cm^2	0.99 (.09) g/cm^2			
Percent change lumbosacral spinal BMD (ITT LOCF)	11/USA	-2.1 %	3.8 %	-6.3 %	3.1 %	4.5 %
	4/F	-0.9 %	5.4 %			
Treatment Effect	11/USA	5.9 %			9.4 %	10.8 %
	4/F	6.3 %				
Postmenopausal bleeding						
• withdrawals	11/USA	0	6%		1.4 %	5.5 %
	4/F	0	4 %			
• AE > 5 %	11/USA	0	11 %	0	1.4 %	6.2 %
	4/F	7 %	11 %			
Breast pain						
• Withdrawals	11/USA	4 %	6 %		2.1 %	2.1 %
	4/F	0	11 %			
• AE > 5 %	11/USA	8 %	17 %	8 %	13.7 %	20.7 %
	4/F	9 %	35 %			

*In NDA 21103 (Activelle, Novo Nordisk), the sponsor proposed only one dose (E2 1 mg NETA 0.5 mg) for the indication of postmenopausal osteoporosis.

**In NDA 21102 (femhrt, Parke Davis), the sponsor proposed two dose combinations (EE 5 mcg NETA 1 mg and [redacted] for the indication of postmenopausal osteoporosis (10/99). Only the EE 5 mcg NETA 1 mg dose combination was approved, as the higher estrogen combination had more adverse events but no statistically greater efficacy in the prevention of osteoporosis.

The subjects in all of the osteoporosis studies were supplemented with calcium, but vitamin D was not supplemented in any of these trials. Approximately the same percentage of women (approximately 80%) were available for the ITT (LOCF) analysis in the different trials, and approximately 70% completed the trials. Bone density was measured by x-ray absorptiometry (DEXA) in the E_2NETA trials and by quantitative computed tomography (QCT) in the EENETA trial. The women in the EENETA (femhrt) trial were closer to the menopause than the women in the E_2NETA trials, and the larger percentage of BMD loss in the placebo group in the EENETA trial may partially reflect the greater bone loss immediately after menopause. Since the E_2NETA and EENETA studies were done at different times with different populations and methodologies, a direct comparison of the efficacy regarding the change in lumbosacral bone mineral density is not possible.

However, the percentage of adverse events, particularly breast pain and postmenopausal bleeding, was much greater in the E_2NETA trials than in the EENETA trial and contributed to a greater number of withdrawals. This difference between E_2 and EE in terms of bleeding has been also reported in an oral contraceptive study of 925 women comparing E_2NETA (E2 (estradiol) 4 mg + E3 (estriol) 2 mg + NETA 3mg) and EENETA (EE 50 mcg NETA 3 mg). Of note, the dosage of the estrogen and progestin are three- to ten-fold greater in the oral contraceptive preparation than in the postmenopausal preparation. Both drugs were similarly effective in pregnancy prevention but E_2NETA was associated with a higher incidence of menstrual irregularities (WHO Task Force on Contraception, Contraception 21(5): 445-59, 1980).

Calcium Intake

The recommended calcium supplement (1000 mg and 500 mg) was less than currently recommended (1200 – 1500 mg qd). Compliance with calcium varied, and low compliance may have contributed to lower BMD efficacy. In additon, absence of vitamin D supplementation may have limited calcium absorption.

Risk of Breast Cancer and Estrogen Progestin Therapy

A meta-analysis of breast cancer and hormone replacement based on 160 000 women who participated in 51 epidemiological studies over 25 years (Collaborative on Hormonal Factors in Breast Cancer. Breast Cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet 350: 1047-59, 1042-44, 1997) concluded an increased relative risk of breast cancer among current or recent users of HRT for more than 5 years. Only 12 % of the hormone users had been exposed to progestins and no conclusions regarding combinations could be drawn. Two recent studies, albeit on a much smaller scale, suggest a possible slightly increased risk of breast cancer with combination estrogen progestin. (Ross et al, 2000; Schairer et al 2000). The sample sizes in these studies and even more so in the clinical trials in this NDA are too small to reach a definitive conclusion at this time.

Preservation of Bone Mineral Density versus Prevention of Fractures

The sponsor cites a two year double blind placebo controlled trial followed by a six year open extension phase in which the group treated with E2 2 mg NETA 1 mg (randomised n=50) had a 14.6% increase in spinal BMD, a group with sequential estrogen progestin had 11.1% increase, while the placebo (randomised n=51) group had a 5.4% decrease over the eight year period. (Eiken et al, 1997) One fracture occurred in the E2NETA group, no fractures occurred in the sequential estrogen progestin group, while 6 fractures occurred in the placebo group. Since less than half of the randomized subjects completed the study, since it was largely open-label, and since the doses of E2NETA were higher than those the sponsor wishes to market, it is difficult to extrapolate the results of these studies to Activelle. Though there is a correlation between BMD and fracture risk, there is no direct translation. Since the current draft osteoporosis guidance has only BMD and not fractures as efficacy measure for osteoporosis prevention and since the populations studies are at relatively low risk for osteoporosis (i.e., mostly not in the lowest quartile of normal bone density), it is not known from these clinical studies whether and/or to what EE 1mg NETA 0.5 mg (or even lower combination doses) may reduce fracture risk.

Population Applicability of Safety Data

1) The study population may not be representative of the larger and more chronically ill target population, and thus more adverse events may be expected in the target population;
2) Whereas women may be willing to tolerate more adverse events for a shorter-term indication, such as relief of hot flushes, paucity of adverse events is important in maintaining compliance with a long-term regimen;
3) Breast pain and postmenopausal bleeding will decrease the compliance with the regimen;
4) Since bleeding is unusual in the postmenopausal population, persistent bleeding will result in anxiety, extra interventions such as medical visits and procedures, and potentially significant additional health care costs.

13 Labeling Recommendations

The FDA labeling recommendations in the postmenopausal osteoporosis section of the Activelle label address the following general concerns:

- presentation of clearer and more complete clinical trial description, including identification of subjects as women with intact uteri, similar descriptions of the subjects in the two multicenter studies in regard to number of years since menopause, and identification of the various treatment arms of the two clinical trials;
- identification of Activelle as 1 mg estradiol and 0.5 mg norethindrone acetate;
- inclusion of Intent to Treat Analysis with Last Observation Carried Forward (not completers) in text and figures; this approach is consistent with ICH guidelines and other estrogen labels for postmenopausal osteoporosis;
- rearrangement of text, table, and figures for greater clarity and easier reading comprehension;

- change in indication to ' [redacted] " is omitted as the two pivotal clinical trials were prevention and not treatment trial, the study populations were women with normal BMD and not osteoporosis, and the outcome was BMD and not fracture.

These specific labeling changes as well as several other syntactic changes are enclosed in the corrected label (see Appendix). In addition, the FDA statistician did not find the placebo-Activelle comparison for Ward's triangle in the European trial to be statistically significant. Please note also that the trade name Activelle™ is not consistently followed by the trademark symbol "™" in the label text.

[These recommendations were discussed at an internal FDA labeling meeting on 3/23/00 and were forwarded with the corrected label electronically to the sponsor.]
In addition, the sponsor was asked to include the comment: "The doses of 17β - estradiol and norethindrone acetate in Activella may not be the lowest effective dose-combination for prevention of osteoporosis" in the label indication section, to emphasize that a lower combination dose may be effective in maintaining bone density and preventing osteoporosis.

14 Recommendations

Approvable – see outstanding concerns below.

The indication of prevention [redacted] of postmenopausal osteoporosis in women with an intact uterus is approvable, pending

1) adequate final sponsor responses to FDA questions;
2) change in labeling, as requested by FDA;
3) additional study of lower estradiol norethindrone acetate combination doses.

Appendixes

- Inclusion/Exclusion Criteria (KLIM/PD/11/USA and KLIM/PD/4/F)
- Completer Efficacy Results
- Safety Data: Withdrawals, Serious Adverse Events, Treatment Emergent Adverse Events in 5% of Population
- Annotated Label Submitted to Sponsor

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/S/

Joanna K. Zawadzki, M.D., F.A.C.P.

Concurrence:

/S/ 4-10-00

Eric Colman, M.D.
Team Leader, Obesity/Osteoporosis Group

SEE TEAM Leader Memo

Distribution:
Archival:HFD580/NDA 20-907; HFD580/Price
HFD510/Hedin/Zawadzki

Inclusion and Exclusion Criteria - KLIM/PD/4/F

Trial Criteria

Inclusion:

- Age (45 ≤ age ≤ 65)
- Natural menopause more than 1 year ago
- BMI ≤ 30 kg/m^2
- Signed informed consent given
- Safety variables within normal range
- E_2 ≤ 30 pg/ml
- FSH > 40 IU/L
- Cervical smear without sign of malignancy (≤ 12 months old)
- Mammography without suspect lesion (≤ 12 months old)
- Normal lumbar BMD (0.80 g/cm^2 ≤ BMD L_{1-4} ≤ 1.20 g/cm^2) *
- Endometrial thickness ≤ 4 mm

Exclusion:

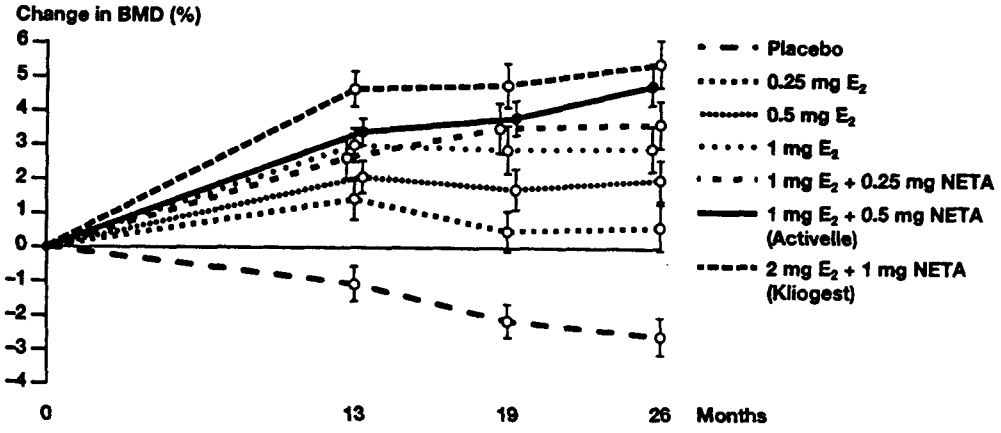
- Known, suspected or past history of breast cancer
- Known, suspected or past history of estrogen dependent cancer, e.g.
  - endometrial cancer
  - endometrioid cancer of the ovary
  - adenocarcinoma of the uterine cervix
- Acute or chronic liver disease or history of liver disease where liver function test have failed to return to normal
- Deep venous thrombosis, thromboembolic disorders, cerebrovascular accidents or past history of these conditions associated with estrogen use
- Abnormal vaginal bleeding of unknown aetiology
- Pituitary tumour
- Diabetes Mellitus
- Thyroid diseases where treatment has not been stable for at least 3 months
- Congestive heart failure, angina pectoris, arrythmia, myocardial infarction
- Systolic blood pressure > 17 cm Hg and/or diastolic blood pressure > 10 cm Hg
- Renal failure
- Medication that could influence the results of the trial:
  - Any estrogen/progestogen treatment within the last 6 months
  - Calcitonin treatment with wash out < 6 months
  - Fluoride treatment for ≥ 6 months or treatment for < 6 months and wash out < 6 months
  - More than 2 courses of bisphosphonate treatment and/or wash out < 6 months
  - Chronic systemic corticosteroid treatment with ≤ 6 months wash out
- Osteoporotic fractures (e.g. non-traumatic vertebral crush fractures)
- Other bone diseases
  - Pagets disease
  - Primary hyperparathyroidism
  - Osteomalacia
- Known lumbar arthrosis with or without lumbar scoliosis
- Porphyria
- Current liver enzyme inducing medication (rifampicin, barbiturates, carbamazepine, phenytoin)
- Known alcohol or drug abuse
- Heavy tobacco consumption (> 2 packs per day)
- Participation in other trials involving other investigational products within the last
  3 months

- corresponding to a t-score between -1.9 SD and +2.0 SD of the mean for healthy young adult women

Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (Completers) - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
n	28	25	24	22	30	24	31
Mean ± SEM	-2.6 ± 0.5	0.6 ± 0.7	2.0 ± 0.6	2.9 ± 0.7	3.6 ± 0.7	4.8 ± 0.6	5.4 ± 0.7

n is the number of women contributing with data for the analysis
SEM: standard error of mean

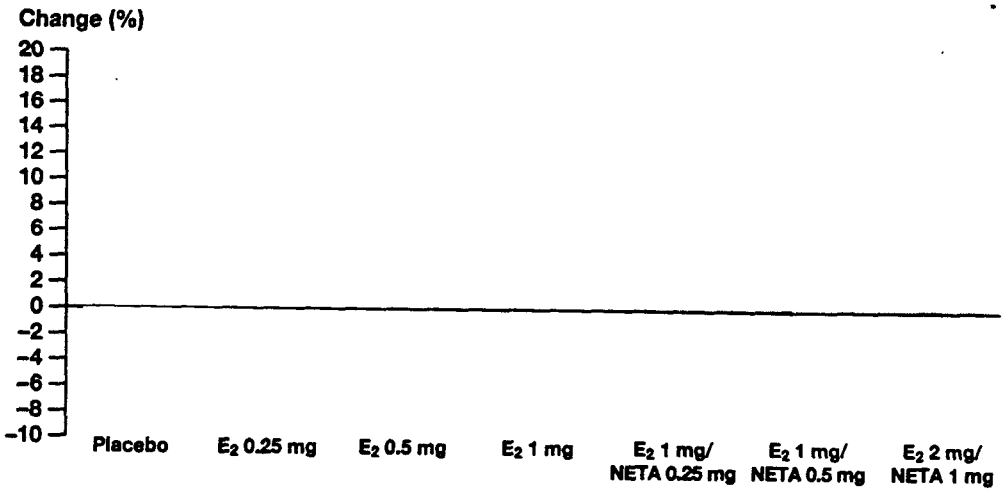


Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) over Time - KLIM/PD/11/USA

Mean Percentage Change in Bone Mineral Density at the Hip (Completers) - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
n	28	25	24	22	29	24	31
Femoral neck Mean ± SEM	-2.6±0.7	0.2±0.8	0.1±0.6	2.4±0.8	2.2±0.5	1.6±0.7	2.9±0.8
Femoral trochanter Mean ± SEM	-2.4±0.8	1.5±1.1	2.2±0.8	3.2±1.0	4.4±0.7	4.3±0.7	5.0±0.9

n is the number of women contributing with data for the analysis



Individual Change in BMD Lumbar Spine - KLIM/PD/11/USA

Responder Analysis I - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1 Kliogest
BMD, lumbar spine							
Change <-2% (loss)	51%	22%	13%	8%	8%	3%	5%
Change -2% to 2%	41%	57%	29%	27%	22%	24%	14%
Change >2% (gain)	8%	22%	58%	65%	70%	73%	81%

Due to rounding off, the percentages may not add up to 100

Responder Analysis II - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
BMD, lumbar spine							
Change <0%	78%	43%	26%	14%	19%	14%	10%
Change ≥0%	22%	57%	74%	87%	81%	87%	91%

Due to rounding off, the percentages may not add up to 100

Mean Percentage Change in Bone Mineral Density at the Lumbar Spine - Distribution by Initial t-score (ITT with LOCF) - KLIM/PD/11/USA

		E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1 + 0.25	1 + 0.5 Activelle	2 + 1
Initial BMD, lumbar spine							
t-score <-1.0 SD (low)							
n	10	6	13	12	9	12	16
Mean change	-1.5%	-0.2%	1.2%	3.2%	2.3%	3.7%	5.8%
Standard error of mean	0.8	1.3	0.8	0.9	1.5	0.8	1.4
t-score >-1.0 SD (normal)							
n	27	31	18	25	28	25	26
Mean change	-2.4%	0.5%	3.0%	2.6%	3.9%	3.9%	4.5%
Standard error of mean	0.6	0.5	0.6	0.6	0.6	0.6	0.7

Mean Percentage Change in Bone Mineral Density at the Lumbar Spine (L_1-L_4) (Completers) - KLIM/PD/4/F

	Placebo		1 mg E_2 + 0.25 mg NETA		1 mg E_2 + 0.5 mg NETA (Activelle)	
Lumbar spine	n=33	-1.1% (0.7)	n=29	5.6% (0.6)	n=29	5.9% (0.9)

Data are provided as mean (standard error of mean)
n is the number of women contributing with data for the analysis

Mean Percentage Change in Bone Mineral Density at the Hip, Distal Radius, and Total Body (Completers) - KLIM/PD/4/F

	Placebo		1 mg E_2 + 0.25 mg NETA		1 mg E_2 + 0.5 mg NETA (Activelle)	
Femoral neck	n=33	-1.2% (0.8)	n=28	1.8% (1.1)	n=29	0.8% (1.2)
Femoral trochanter	n=33	0.5% (1.2)	n=28	4.0% (1.2)	n=28	6.6% (1.5)
Ward's triangle	n=33	-1.9% (1.6)	n=28	2.9% (1.8)	n=28	2.3% (2.1)
Distal radius	n=32	-0.5% (0.5)	n=29	1.0% (0.6)	n=27	2.1% (0.6)
Total body	n=32	0.5% (0.4)	n=28	2.7% (0.6)	n=27	3.7% (0.6)

Data are provided as mean (standard error of mean)
n is the number of women contributing with data for the analysis

Responder Analysis I - KLIM/PD/4/F

	Placebo	1 mg E2 + 0.25 mg NETA	1 mg E2 + 0.5 mg NETA (Activelle)
BMD, lumbar spine			
Change <-2% (loss)	40%	0%	5%
Change -2% to 2%	33%	22%	21%
Change >2% (gain)	28%	78%	74%

Due to rounding off, the percentages may not add up to 100

Responder Analysis II - KLIM/PD/4/F

	Placebo	1 mg E_2 + 0.25 mg NETA	1 mg E_2 + 0.5 mg NETA (Activelle)
BMD, lumbar spine			
Change <0%	63%	8%	13%
Change ≥0%	38%	92%	87%

Due to rounding off, the percentages may not add up to 100

Adverse Events Leading to Discontinuation - KLIM/PD/11/USA

Treatment	Center/ Subject ID	Adverse event(s)
Placebo	1/16	Hot flushes
	5/344	Endometrial hyperplasia
	6/109	Pruritus
	6/113	Hot flushes
	8/162	Hot flushes
	10/204	Hot flushes
	11/225	Stomatitis ulcerative, tendinitis, leukorrhoea, breast pain female, libido increased, endometrial disorder
	12/238	Cramps legs, sweating increased, insomnia
	13/393	Gastroenteritis
	15/301	Insomnia, nervousness, pain, pruritus
	15/305	Other events, breast pain female
0.25 mg E_2	1/1	Dizziness
	1/17	Breast neoplasm malignant
	2/29	Weight increase
	4/68	Pituitary neoplasm nos
	5/347	Abdominal pain
	5/355	Abdominal pain
	6/123	Uterine fibromyoma, endometrial hyperplasia, endometriosis
	8/160	Other events
	12/242	Weight increase, alopecia, chest pain
0.5 mg E_2	5/339	Weight increase
	5/346	Abdominal pain
	5/356	Uterovaginal prolapse

Adverse Events Leading to Discontinuation - KLIM/PD/11/USA - continued

Treatment	Center/ Subject ID	Adverse event(s)
1 mg E_2	2/33	Hot flushes
+0.25 mg NETA	5/342	Breast pain female, edema generalized
	6/106	Post-menopausal bleeding
	6/408	Neoplasm (ovarian endometrioma)
	13/265	Headache
	13/388	Post-menopausal bleeding
	14/283	Depression, libido decreased, somnolence, dyspepsia
1 mg E_2	1/12	Breast pain female
+ 0.5 mg NETA	3/56	Post-menopausal bleeding
(Activelle)	6/107	Post-menopausal bleeding
	7/127	Abdominal pain
	12/233	Adenocarcinoma nos, adenocarcinoma nos
	13/396	Breast pain female, post-menopausal bleeding
	14/282	Emotional lability, nausea, edema generalized
	16/317	Breast pain female, emotional lability, flatulence
2 mg E_2	4/64	Breast disorder nos
+ 1 mg NETA	5/348	Herpes zoster
	6/126	Post-menopausal bleeding
	11/212	Post-menopausal bleeding, endometrial disorder, uterine fibroid
	11/221	Skin discoloration, post-menopausal bleeding, uterine fibroid
	12/236	Breast pain female, breast pain female, abdominal pain, constipation, diarrhea, flatulence
	12/400	Post-menopausal bleeding
	15/299	Breast pain female, abdominal pain, post-menopausal bleeding

Adverse Events Leading to Discontinuation - KLIM/PD/4/F

Subject ID	Exposure (days)	Adverse event leading to discontinuation	Severity	Relation to drug	Outcome
Placebo					
7	31	migraine aggravated	mild	probable	rec. compl.
41	189	fracture, vertebral fract.	severe	unlikly	rec. w. seq.
67	471	fracture, fracture of L_1	moderate	unknown	rec. w. seq.
79	7	nervousness	mild	unknown	not yet rec.
98	23	nausea	mild	probable	rec. compl.
122	203	cardiomyopathy	severe	unlikely	death
1 mg E_2 + 0.25 mg NETA					
2	327	migraine	moderate	probable	rec. compl.
3	71	hypertriglyceridaemia	moderate	possible	not yet rec.
21	496	thrombophlebitis leg	severe	possible	rec. compl.
28	5	breast pain	mild	probabale	rec. compl.
46	293	postmenopausal bleeding	moderate	probable	rec. compl.
59	265	postmenopausal bleeding	moderate	possible	rec. compl.
75	32	breast pain	mild	probable	rec. compl.
83	244	hypertension	moderate	possible	rec. compl.
95	349	thrombophlebitis superf.	moderate	unknown	rec. w. seq.
100	65	malaise	mild	possible	rec. compl.
103	61	phlebitis	severe	possible	rec. compl.
1 mg E_2 + 0.5 mg NETA (Activelle)					
1	27	breast pain	moderate	probable	rec. compl.
	158	headache	mild	unlikely	rec. compl.
12	53	postmenopausal bleeding leading to hospitalisation for curettage	moderate	possible	rec. compl.
13	196	asthenia	severe	possible	rec. compl.
16	76	benign breast neoplasm	moderate	possible	stabilised
25	126	myocardial infarction	severe	unlikely	death
47	9	breast pain	moderate	probable	rec. compl.
48	354	cervical uterine polyp	moderate	possible	rec. compl.
77	375	malignant neoplasm, hepatic cancer	severe	unlikely	stabilised
80	8	migraine	moderate	possible	rec. compl.
97	0	breast pain	moderate	N/A	unknown
106	28	headache and breast pain	mild	possible	rec. compl.
134	23	breast pain	mild	possible	rec. compl.
136	179	breast fibroadenosis	mild	possible	unknown

Adverse Events Leading to Discontinuation - KLIM/PD/19/USA

Subject ID	Exposure (days)	Adverse event leading to discontinuation	Severity	Relation to drug	Outcome
Placebo					
1144	64	flu	moderate	unlikely	recovered
	80	viral infection	moderate	unlikely	recovered
1182	23	hypertension	moderate	possible	recovered
1227	127	hair loss	severe	unknown	recovered
1 mg E_2					
1216	-23 *	insomnia	moderate	unknown	recovered
	15	whole body bloating	moderate	probable	recovered
1240	49	heavy vaginal bleeding	moderate	probable	recovered
1 mg E_2 + 0.25 mg NETA					
1125	4	infected breast cyst L	severe	unknown	recovered
1133	84	heavy spotting	moderate	probable	recovered
1152	52	vaginal bleeding	moderate	probable	recovered
1161	8	L lower side and back pain	moderate	unlikely	rec. w. seq.
1209	45	vaginal spotting	moderate	probable	recovered
1231	16	fever blisters	moderate	unlikely	not yet rec.
1 mg E_2 + 0.5 mg NETA (Activelle)					
1018	18	dizziness	moderate	unknown	recovered
	18	sluggishness	moderate	unknown	recovered
	18	agitation	moderate	unknown	recovered
	18	inability to think clearly	moderate	unknown	recovered
	18	bloating	moderate	unknown	recovered
	18	nausea	moderate	unknown	recovered
1036	17	breast tenderness	moderate	probable	recovered
	22	bloating	moderate	probabale	recovered
	22	edema	moderate	probable	recovered
1153	116	alopecia	severe	possible	not yet rec.
1212	126	lung cancer	severe	unlikely	death
1266	44	bleeding/spotting mild	mild	probable	recovered
	60	bleeding/spotting moderate	moderate	probable	recovered

* insomnia began after screening but before exposure to trial product

Serious Adverse Events - KLIM/PD/11/USA

Subject ID	IPS case	Exposure (days)	Serious adverse event (preferred term)	Severity	Relation to drug	Outcome
Placebo						
344 *	105386	363	endometrial hyperplasia	severe	possible	not yet rec.
0.25 mg E_2						
17 *	106665	495	breast neoplasm malignant female	severe	probable	not yet rec.
68	108041	631	pituitary neoplasm benign	moderate	unlikely	not yet rec.
123 *	106847	167	uterine fibroid	moderate	possible	rec. completely
123 *	106847	167	endometriosis	N/A	possible	N/A
123 *	106847	167	endometrial hyperplasia	N/A	possible	N/A
154	103364	130	other events	moderate	unlikely	rec. completely
198	107412	592	back pain	severe	unlikely	not yet rec.
0.5 mg E_2						
13	107479	510	infection viral	severe	unlikely	rec. completely
13	107479	571	back pain	severe	unlikely	rec. completely
318	104151	252	cholelithiasis	moderate	possible	rec. completely
356	106603	361	uterovaginal prolapse	severe	unlikely	rec. completely
1 mg E_2						
34	106027	375	injury accidental	severe	unlikely	rec. completely
59	109107	738	breast neoplasm malignant female	severe	possible	not yet rec.
130	105875	484	endometrial hyperplasia	severe	possible	rec. completely
1 mg E_2 + 0.25 mg NETA						
408	106495	365	endometriosis	moderate	possible	rec. completely
1 mg E_2 + 0.5 mg NETA (Activelle)						
193	105173	191	nausea	mild	unlikely	rec. completely
193	105173	191	vomiting	mild	unlikely	rec. completely
201	106583	422	injury accidental	severe	unlikely	not yet rec.
233 *	105802	284	adenocarcinoma nos	severe	unlikely	death **
429	105201	168	asthma	severe	unlikely	rec. completely
2 mg E_2 + 1 mg NETA						
101	108268	588	cyst nos	moderate	unlikely	rec. completely
326	105602	187	endometrial disorder	moderate	possible	not yet rec.

N/A: not available
* the woman discontinued from the trial because of the adverse event
** this case was described in chapter **Error! Reference source not found.**

Serious Adverse Events - KLIM/PD/4/F

Subject ID	IPS case	Exposure (days)	Serious adverse event (preferred term)	Severity	Relation to drug	Outcome
Placebo						
8	104749	504	anxiety	moderate	unlikely	rec. completely
14	104654	523	vertigo	moderate	unlikely	rec. w. sequelae
41 *	102668	189	fracture bone	severe	unlikely	rec. w. sequelae
45	106329	468	renal calculus	moderate	unlikey	rec. completely
51	104270	343	uterine neoplasm	moderate	possible	rec. completely
67 *	106582	471	fracture bone	moderate	unknown	rec. w. sequelae
74	105042	365	fracture bone	mild	unknown	rec. completely
122 *	105178	203	cardiomyopathy	severe	unlikly	death **
1 mg E_2 + 0.25 mg NETA						
2	101744	327	hypertension	severe	probable	rec. w. sequelae
2	101744	327	migraine	moderate	probable	rec. completely
2	106170	755	diverticulitis	severe	unlikely	rec. completely
11	102962	170	ovarian cyst	moderate	possible	rec. completely
28	103515	430	hearing decreased	severe	unlikely	rec. w. sequelae
28	103515	430	vascular disorder	severe	probable	rec. completely
33	104487	258	injury accidental	moderate	unlikely	rec. w. sequelae
43	105971	562	cellulitis	moderate	unlikely	rec. completely
72	106880	478	sinusitis	mild	unlikely	rec. w. sequelae
72	107186	593	injury accidental	severe	unlikely	rec. w. seqeulae
76	106147	443	depression	severe	unlikely	rec. w. sequelae
82	105240	98	back pain	moderate	unlikely	not yet rec.
103	104384	61	phlebitis	severe	possible	rec. completely
135	108556	201	blepharospasm	moderate	unlikely	rec. completely
1 mg E_2 + 0.5 mg NETA (Activelle)						
12	102763	53	postmenopausal bleeding	moderate	possible	rec. completely
25	100474	126	myocardial infarction	severe	unlikely	death **
48	105970	354	cervical uterine polyp	moderate	possible	rec. completely
55	106099	544	uterovaginal prolapse	mild	unlikely	rec. completely
77	106145	375	neoplasm malignant	severe	unlikely	stabilised
85	106129	348	cholecystitis	moderate	unlikely	rec. completely
117	105275	105	uterine neoplasm	moderate	probable	rec. completely
125	106865	450	verruca	severe	unlikely	rec. completely

* the woman discontinued from the trial because of the adverse event
** these cases were described in chapter **Error! Reference source not found.**

Serious Adverse Events - KLIM/PD/19/USA

Subject ID	IPS case	Exposure (days)	Serious adverse event (preferred term)	Severity	Relation to drug	Outcome
Placebo						
159	106340	178	breast neoplasm malignant female	moderate	unlikely	recovered
1 mg E_2 + 0.25 mg NETA						
015	105693	197	cervix carcinoma	severe	unlikely	recovered
058	105135	117	dehydration	mild	unlikely	recovered
058	105135	117	influenza-like symptoms	severe	unlikely	recovered
268	106038	175	cellulitis	severe	unlikely	recovered
1 mg E_2 + 0.5 mg NETA (Activelle)						
212	105678	126	pulmonary carcinoma	severe	unlikely	death

Treatment-emergent Adverse Events Reported by ≥5% of Women in a Treatment Group - KLIM/PD/11/USA

		Unopposed E_2 (mg)			E_2 + NETA (mg)		
	Placebo	0.25	0.5	1	1+0.25	1+0.5 Activelle	2+1
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Women randomised	48	45	44	46	49	47	48
Adverse events	41(85)	39(87)	36(82)	40(87)	40(82)	39(83)	45(94)
BODY AS A WHOLE							
Back pain	2(4)	3(7)	4(9)	2(4)	4(8)	3(6)	4(8)
Abdominal pain	0	4(9)	5(11)	1(2)	1(2)	2(4)	2(4)
Hot flushes	4(8)	1(2)	1(2)	2(4)	0	1(2)	0
Pain	4(8)	1(2)	1(2)	1(2)	4(8)	1(2)	0
CARDIOVASCULAR DISORDERS							
Hypertension	4(8)	5(11)	0	0	1(2)	1(2)	5(10)
CNS & PERIPHERAL SYSTEM							
Headache	3(6)	6(13)	1(2)	5(11)	4(8)	5(11)	1(2)
Dizziness	0	1(2)	4(9)	1(2)	1(2)	2(4)	0
GASTRO-INTESTINAL SYSTEM							
Nausea	0	1(2)	1(2)	0	0	5(11)	0
Gastroenteritis	2(4)	0	0	0	1(2)	3(6)	0
Constipation	3(6)	1(2)	0	3(7)	2(4)	2(4)	0
Diarrhoea	1(2)	1(2)	0	4(9)	1(2)	2(4)	1(2)
Flatulence	1(2)	1(2)	4(9)	1(2)	2(4)	2(4)	0
Abdominal pain	1(2)	3(7)	0	3(7)	0	1(2)	2(4)
Dyspepsia	2(4)	0	1(2)	3(7)	2(4)	1(2)	0
Tooth disorder	1(2)	1(2)	0	1(2)	3(6)	0	1(2)
METABOLIC AND NUTRITIONAL							
Weight increase	3(6)	2(4)	3(7)	3(7)	2(4)	4(9)	4(8)
MUSCULO-SKELETAL							
Arthralgia	3(6)	3(7)	4(9)	4(9)	2(4)	2(4)	1(2)
Fracture pathological	0	4(9)	0	0	0	0	2(4)
NEOPLASM							
Cervical uterine polyp	2(4)	0	0	1(2)	0	3(6)	3(6)
Uterine fibroid	4(8)	8(18)	3(7)	10(22)	3(6)	2(4)	14(29)
Breast fibroadenosis	0	0	1(2)	1(2)	0	1(2)	3(6)
Cervical smear test pos.	2(4)	3(7)	0	1(2)	0	1(2)	2(4)
Ovarian cyst	4(8)	5(11)	4(9)	4(9)	2(4)	0	2(4)
PSYCHIATRIC DISORDERS							
Emotional lability	0	0	0	1(2)	0	3(6)	0
Depression	0	0	0	2(4)	4(8)	1(2)	1(2)
Anxiety	0	0	0	4(9)	1(2)	0	2(4)
Imsomnia	4(8)	1(2)	1(2)	0	0	0	1(2)
REPRODUCTION DISORDERS							
Breast pain female	4(8)	1(2)	2(5)	4(9)	5(10)	8(17)	6(13)
Postmenopausal bleeding	0	1(2)	3(7)	9(20)	3(6)	5(11)	6(13)
Breast disorder nos	1(2)	0	1(2)	3(7)	1(2)	0	1(2)
Endometrial disorder	3(6)	2(4)	4(9)	12(26)	1(2)	0	4(8)
Endometrial hyperplasia	1(2)	1(2)	1(2)	6(13)	0	0	0
RESISTANCE MECHANISM							
Infection viral	3(6)	4(9)	3(7)	2(4)	4(8)	3(6)	4(8)
Moniliasis genital	0	1(2)	1(2)	1(2)	4(8)	3(6)	3(6)
RESPIRATORY SYSTEM							
Sinusitis	5(10)	5(11)	3(7)	6(13)	3(6)	7(15)	2(4)
Upper resp tract inf	9(19)	6(13)	10(23)	8(17)	7(14)	7(15)	10(21)
Coughing	2(4)	0	0	1(2)	1(2)	2(4)	3(6)
Bronchitis	1(2)	4(9)	1(2)	0	1(2)	0	3(6)
SECONDARY TERMS							
Injury accidental	2(4)	2(4)	1(2)	6(13)	7(14)	8(17)	4(8)
Other events	2(4)	4(9)	1(2)	1(2)	3(6)	3(6)	3(6)
Cyst nos	1(2)	2(4)	3(7)	4(9)	3(6)	2(4)	3(6)
Bite	0	1(2)	3(7)	0	0	0	0
SKIN AND APPENDAGES							
Rash	2(4)	1(2)	4(9)	0	1(2)	1(2)	2(4)

N = number of subjects
% = proportion of exposed subjects having the event

Treatment-emergent Adverse Events Reported by ≥5% of Women in a Treatment Group - KLIM/PD/4/F

System Organ Class (WHO)	Placebo N	(%)	E	1 mg E_2 +0.25 mg NETA N	(%)	E	1 mg E_2 +0.5 mg NETA Activelle N	(%)	E
Subjects Exposed	45			44			46		
All Adverse Events	43	(96%)	176	44	(100%)	225	40	(87%)	230
BODY AS A WHOLE - GENERAL									
Back pain	8	(18%)	9	8	(18%)	11	13	(28%)	15
Influenza-like symptoms	5	(11%)	7	4	(9%)	4	11	(24%)	15
Asthenia	1	(2%)	1	1	(2%)	1	5	(11%)	5
Headache	2	(4%)	2	0			5	(11%)	5
Pain	9	(20%)	10	5	(11%)	5	5	(11%)	5
Allergy	0			0			4	(9%)	4
Leg pain	1	(2%)	1	3	(7%)	3	4	(9%)	4
Weight increase	0			2	(5%)	2	3	(7%)	3
Hot flushes	4	(9%)	4	0			0		
Oedema	0			2	(5%)	2	0		
CARDIOVASCULAR DISORDERS, GENERAL									
Hypertension	2	(4%)	2	3	(7%)	3	3	(7%)	3
CENTR & PERIPH NERVOUS SYSTEM									
Migraine	2	(4%)	2	2	(5%)	2	2	(4%)	2
Vertigo	4	(9%)	4	3	(7%)	3	2	(4%)	2
Paraesthesia	1	(2%)	2	2	(5%)	2	1	(2%)	1
Headache	0			2	(5%)	2	0		
GASTRO-INTESTINAL SYSTEM									
Abdominal pain	2	(4%)	2	5	(11%)	6	4	(9%)	4
Nausea	2	(4%)	2	2	(5%)	2	3	(7%)	3
Gastroenteritis	3	(7%)	3	2	(5%)	2	2	(4%)	2
Tooth disorder	3	(7%)	3	1	(2%)	1	0		
METABOLIC AND NUTRITIONAL									
Hypercholesterolaemia	9	(20%)	12	10	(23%)	12	6	(13%)	6
Weight increase	0			2	(5%)	2	3	(7%)	3
Hypertriglyceridaemia	3	(7%)	3	2	(5%)	2	0		
MUSCULO-SKELETAL SYSTEM									
Arthrosis	0			3	(7%)	5	1	(2%)	1
Fracture bone	4	(9%)	4	1	(2%)	1	0		
Tendinitis	2	(4%)	2	3	(7%)	3	0		
PSYCHIATRIC DISORDERS									
Depression	1	(2%)	1	2	(5%)	2	4	(9%)	5
Anxiety	5	(11%)	5	2	(5%)	4	2	(4%)	2
Insomnia	3	(7%)	3	0			1	(2%)	1

N = number of subjects
% = proportion of exposed subjects having the event
E = number of adverse events

Treatment-emergent Adverse Events Reported by ≥5% of Women in a Treatment Group - KLIM/PD/4/F - continued

System Organ Class (WHO)	Placebo N	(%)	E	1 mg E_2 +0.25 mg NETA N	(%)	E	1 mg E_2 +0.5 mg NETA Activelle N	(%)	E
REPRODUCTIVE DISORDERS, FEMALE									
Breast pain female	4	(9%)	4	17	(39%)	20	16	(35%)	18
Postmenopausal bleeding	3	(7%)	3	13	(30%)	17	6	(11%)	9
Vaginitis	1	(2%)	1	3	(7%)	4	4	(9%)	4
Leukorrhoea	0			2	(5%)	2	1	(2%)	1
Vaginal haemorrhage *	0			1	(2%)	1	1	(2%)	1
RESISTANCE MECHANISM DISORDERS									
Otitis media	0			0			3	(7%)	3
Herpes simplex	3	(7%)	3	2	(5%)	6	0		
Herpes zoster	3	(7%)	3	3	(7%)	3	0		
RESPIRATORY SYSTEM DISORDERS									
Bronchitis	2	(4%)	4	4	(9%)	4	7	(15%)	8
Pharyngitis	3	(7%)	3	4	(9%)	5	4	(9%)	4
Rhinitis	2	(4%)	2	4	(9%)	5	3	(7%)	3
Dyspnoea	0			2	(5%)	2	0		
Laryngitis	0			2	(5%)	2	0		
Sinusitis	2	(4%)	2	5	(11%)	7	0		
SECONDARY TERMS									
Injury accidental	5	(11%)	5	5	(11%)	6	3	(7%)	3
SKIN AND APPENDAGES DISORDERS									
Pruritus	0			3	(7%)	4	2	(4%)	2
URINARY SYSTEM DISORDERS									
Urinary incontinence	1	(2%)	1	2	(5%)	2	2	(4%)	4
Urinary tract infection	3	(7%)	4	2	(5%)	2	2	(4%)	2
VASCULAR (EXTRACARDIAC) DISORDERS									
Vein varicose	2	(4%)	2	5	(11%)	5	3	(7%)	3
Thrombophlebitis superficial	0			2	(5%)	2	0		

N = number of subjects
% = proportion of exposed subjects having the event
E = number of adverse events
* = vaginal haemorrhage is included as it will be presented with postmenopausal bleeding

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ON ORIGINAL

All Treatment-emergent Adverse Events - KLIM/PD/18/J

System Organ Class	Placebo			1 mg E_2 +0.5 mg NETA Activelle			2 mg E_2 +1 mg NETA		
	N	(%)	E	N	(%)	E	N	(%)	E
Subjects Exposed	16			16			15		
All Adverse Events	2	(13%)	2	12	(75%)	19	10	(67%)	15
BODY AS A WHOLE - GENERAL DISORDERS									
Fever	0			0			1	(7%)	1
CENTRAL & PERIPH NERVOUS SYSTEM									
Unconsciousness	0			1	(6%)	1	0		
Numbness of upper arm	0			0			1	(7%)	1
GASTRO-INTESTINAL SYSTEM									
Nausea	0			1	(6%)	1	0		
Constipation	0			0			1	(7%)	1
METABOLIC & NUTRITIONAL									
Increased blood sugar	0			1	(6%)	1	0		
Oedema of lower extremities	0			1	(6%)	1	0		
Thirst	0			1	(6%)	1	0		
Increased triglycerides	1	(6%)	1	0			0		
PLATELET, BLEEDING & CLOTTING									
Increased fibrinogen	0			0			1	(7%)	1
REPRODUCTIVE DISORDERS									
Bleeding	0			4	(25%)	6	6	(40%)	6
Change in cervical smear	0			1	(6%)	1	0		
Mastalgia	0			1	(6%)	1	2	(13%)	2
Breast swelling	0			1	(6%)	1	2	(13%)	2
Vaginal discharge	0			1	(6%)	1	0		
Mastopathy	0			0			1	(7%)	1
SKIN & APPENDAGES									
Eczema	1	(6%)	1	1	(6%)	2	0		
URINARY SYSTEM									
Positive urinary sugar	0			1	(6%)	1	0		
WHITE CELL & RESISTANCE									
Eosinophilia	0			1	(6%)	1	0		

N = number of subjects
% = proportion of exposed subjects having the event
E = number of adverse events

Treatment-emergent Adverse Events Reported by ≥5% of Women in a Treatment Group - KLIM/PD/19/USA

System Organ Class (WHO)	Placebo N	(%)	1 mg E2 N	(%)	1 mg E2 +0.25 mg NETA N	(%)	1 mg E2 +0.5 mg NETA Activelle N	(%)
Subjects exposed	68		67		68		67	
All adverse events	52	77%	58	87%	61	90%	62	93%
BODY AS A WHOLE								
Abdominal pain	6	9%	8	12%	5	7%	7	10%
Hot flushes	8	12%	3	4%	0		2	3%
Pain	5	7%	3	4%	2	3%	4	6%
CENTRAL & PERIPH NERVOUS SYSTEM								
Headache	1	1%	5	7%	5	7%	6	9%
Dizziness	5	7%	0		1	1%	3	4%
GASTRO-INTESTINAL SYSTEM								
Flatulence	5	7%	7	10%	9	13%	7	10%
Diarrhoea	1	1%	1	1%	4	6%	0	
PSYCHIATRIC DISORDERS								
Insomnia	0		5	7%	2	3%	2	3%
REPRODUCTIVE DISORDERS, FEMALE								
Breast pain female	5	7%	22	33%	25	37%	34	51%
Postmenopausal bleeding	5	7%	16	24%	23	34%	23	34%
Leukorhoea	2	3%	16	24%	11	16%	14	21%
RESISTANCE MECHANISM DISORDERS								
Infection viral	9	13%	3	4%	5	7%	6	9%
Moniliasis genital	0		5	7%	4	6%	4	6%
Infection	4	6%	3	4%	2	3%	3	4%
RESPIRATORY SYSTEM DISORDERS								
Upper resp tract infection	14	21%	18	27%	9	13%	13	19%
Sinusitis	3	4%	1	1%	6	9%	3	4%
SKIN & APPENDAGES DISORDERS								
Pruritus genital	0		8	12%	1	1%	3	4%

N = number of subjects
% = proportion of exposed subjects having the event
E = number of adverse events

All Treatment-emergent Adverse Events - KLIM/PD/15/IRL

System Organ Class (WHO)	1 mg E_2 N	(%)	E	1 mg E_2 + 0.5 mg NETA Activelle N	(%)	E
Women exposed	19			19		
Adverse events	4	(21%)	6	7	(37%)	11
BODY AS A WHOLE - GENERAL DISORDERS						
Back pain	0			1	(5%)	1
Chest pain	0			1	(5%)	1
Headache	0			1	(5%)	1
Pain	0			1	(5%)	1
CENTR & PERIPH NERVOUS SYSTEM DISORDERS						
Paraesthesia	0			1	(5%)	1
Speech disorder	0			1	(5%)	1
GASTRO-INTESTINAL SYSTEM DISORDERS						
Vomiting	1	(5%)	1	0		
REPRODUCTIVE DISORDERS, FEMALE						
Breast pain female	0			2	(11%)	2
Vaginal discomfort	0			1	(5%)	1
Endometrial hyperplasia	1	(5%)	1	0		
Leukorrhoea	1	(5%)	1	0		
SKIN AND APPENDAGES DISORDERS						
Skin disorder	1	(5%)	1	0		
URINARY SYSTEM DISORDERS						
Dysuria	0			1	(5%)	1
Urinary tract infection	2	(11%)	2	1	(5%)	1

N = number of subjects
% = proportion of exposed subjects having the event
E = number of adverse events

31 pages redacted from this section of the approval package consisted of draft labeling