

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-885

MEDICAL REVIEW

MEDICAL TEAM LEADER REVIEW

NDA: 21-885

DRUG: Climara Pro (17-beta estradiol/levonorgestrel) Transdermal

INDICATION: Prevention of Postmenopausal Osteoporosis

COMPANY: Berlex

PRIMARY CLINICAL REVIEWERS: Bruce Stadel, MD, and Brenda Gierhart, MD

STATISTICAL REVIEWER: Joy Mele, MS

PDUFA GOAL DATE: January 1, 2006

I. REGULATORY RECOMMENDATION OF PRIMARY REVIEWS: Approve.

II. BACKGROUND

Climara Pro [0.045 mg estradiol /0.015 mg levonorgestrel per day (22 sq cm)] matrix transdermal system was approved on November 21, 2003, for the treatment of moderate-to-severe vasomotor symptoms associated with menopause. Each patch is to be worn for a one-week period.

With this submission, Berlex is requesting approval of Climara Pro for the prevention of postmenopausal osteoporosis (PMO).

During an October 13, 2004 Pre-NDA meeting, Berlex asked if it was acceptable to pursue approval of the Climara Pro patch based on a pivotal study (A09585) of an estradiol-only patch and supportive data from a phase 3 study (A10079) that used a estradiol/levonorgestrel patch? The Division replied that Berlex's proposal was acceptable.

See Dr. Stadel's review for additional comments made during the Pre-NDA meeting.

III. CLINICAL DATA

Study A09585 investigated the effects of 0.022 mg/day and 0.045 mg/day of transdermal estradiol to placebo on lumbar spine (LS) bone mineral density (BMD) in postmenopausal women without osteoporosis. Data from this trial provide evidence that the 0.045 mg/day transdermal estradiol significantly increases LS BMD compared with placebo.

Study A10079 investigated the effects of 0.045 mg/day estradiol/30 mcg/day levonorgestrel and 0.045 mg/day estradiol/40 mcg/day levonorgestrel (transdermal) to placebo on LS BMD in postmenopausal women without osteoporosis. Data from this trial provide evidence that the addition of levonorgestrel does not attenuate the bone effects of 0.045 mg/day estradiol.

As agreed upon at the Pre-NDA meeting, the data from trial A09585 provide the majority of the information upon which approval of this supplemental NDA and its labeling is based. No data from study A10079 have been proposed for inclusion in the labeling.

IV. SYNOPSIS OF STUDY A09585

This was a randomized, double-blind, placebo-controlled 2-year trial. Subjects without a uterus were randomized (2:2:3) to 0.022 mg/day, 0.045 mg/day, or placebo transdermal estradiol. Based on a dietary calcium survey at baseline, patients received supplements sufficient for their total daily calcium intake to be about 1500 mg; women whose estimated dietary calcium intake was > 1500 mg/day did not receive calcium supplementation. Vitamin D supplements were not provided.

The primary efficacy variable was the percent change from baseline to Endpoint in LS BMD. The secondary variables included percent change in BMD of the non-dominant radius and total hip; the proportions of women with no loss from baseline of LS BMD and total hip; and the absolute changes in biochemical markers of bone turnover.

The pre-defined efficacy analysis population consisted of patients in the modified ITT group who did not erroneously switch study drug during the trial.

A total of 62, 45, and 47 subjects were randomized to placebo, 0.022 mg, and 0.045 mg transdermal estradiol. The groups were well-matched for baseline demographic characteristics. The mean age was 51 years; 77% were Caucasian; the average years since menopause was 10.5; mean estradiol was 8 pg/ml; and the average LS BMD was 1.1 g/cm².

A total of 27, 25, and 22 subjects from the placebo, 0.022 mg, and 0.045 mg groups completed the 2-year study. Approximately 26%, 16%, and 16% of the placebo, 0.022 mg, and 0.045 mg subjects withdrew from the trial due to adverse events.

In the primary efficacy population, the mean percent changes in LS BMD from baseline to Endpoint were -2.8%, 0.42%, and 2.1% in the placebo, 0.022 mg, and 0.045 mg groups, respectively (p<0.001 both estradiol doses vs placebo). In the completers population, the mean percent changes in LS BMD were -3.3%, 0.38%, and 2.6% in the placebo, 0.022 mg, and 0.045 mg groups, respectively (p=0.004, 0.022 mg vs. placebo and p<0.001, 0.045 mg vs. placebo).

In the primary efficacy population, the mean percent changes in total hip BMD from baseline to Endpoint were -0.85%, -0.19%, and 1.4% in the placebo, 0.022 mg, and 0.045

mg groups, respectively ($p=0.2$, 0.022 vs. placebo, and $p=0.007$, 0.045 vs. placebo). In the completers population, the mean percent changes in total hip BMD were -0.05% , -0.72% , and 2.1% in the placebo, 0.022 mg, and 0.045 mg groups, respectively ($p=0.5$, 0.022 vs. placebo, and $p=0.08$, 0.045 vs. placebo).

In the primary efficacy population, the mean percent changes in radius BMD from baseline to Endpoint were -0.5% , 0.5% , and -0.5% in the placebo, 0.022 mg, and 0.045 mg groups, respectively ($p=NS$ for both active groups vs. placebo).

The biochemical marker of bone resorption decreased in the 0.022 mg and 0.045 mg groups relative to placebo, but the differences between the estradiol and placebo groups were not statistically significant. The biochemical marker of bone formation decreased in the 0.022 mg and 0.045 mg groups relative to placebo and the differences between both active doses and placebo were statistically significant.

The LS BMD data were also analyzed according to baseline endogenous estradiol levels. Estimated treatment effects were approximately twice as large in the subgroup with estradiol levels < 5 pg/ml compared with the subgroup with endogenous estradiol levels ≥ 5.0 pg/ml.

See Dr. Stadel's review for results of other secondary efficacy variables.

Dr. Stadel did not identify any meaningful or unexpected safety signals from this study.

V. SYNOPSIS OF STUDY A10079

This was a randomized, double-blind, placebo-controlled 2-year trial conducted in Denmark. Subjects were randomized (1:1:1) to 0.045 mg estradiol/ 40 mcg levonorgestrel per day (0.045 mg group), 0.044 mg estradiol/ 30 mcg levonorgestrel per day (0.044 mg group), or placebo. All patients were instructed to take 500 mg elemental supplemental calcium per day. Vitamin D supplements were not prescribed.

The primary efficacy variable was the mean percent change from baseline to Endpoint in LS BMD. Secondary variables included percent changes from baseline in BMD of the hip, non-dominant radius, and total body; and the absolute changes in biochemical markers of bone turnover. The primary efficacy analysis was conducted in two subgroups: A: women who were more than one and up to three years postmenopausal and B: women who were more than three and up to 10 years postmenopausal.

A total of 71 women were randomized to the 0.044 mg group, 72 to the 0.045 mg group, and 71 to the placebo group. The groups were well-matched for baseline demographic characteristics. The mean age was 55 years; 99% of the women were Caucasian; the average BMI was 25 kg/m²; and the mean LS BMD T-score was -1.2 .

A total of 33, 32, and 45 of the women in the 0.044 mg, 0.045 mg, and placebo groups, respectively, completed the 2-year study. Adverse events accounted for the greatest percentage of premature withdrawals.

In subgroup A, the mean percent changes in LS BMD from baseline to Endpoint were 3.8%, 4.2%, and -2.6% in the 0.044 mg, 0.045 mg, and placebo groups, respectively. In subgroup B, the mean percent changes in LS BMD from baseline to Endpoint were 4.6%, 5.2%, and -1.6% in the 0.044 mg, 0.045 mg, and placebo groups, respectively. All active drug vs. placebo comparisons were statistically significant.

According to Dr. Stadel, at the hip and total body, but not the radius, BMD increased in both active-dose groups relative to placebo. The changes in biochemical markers of bone turnover were supportive of the antiresorptive effect of estrogen/progestin.

There were no unexpected safety findings in this trial

VI. SUMMARY OF EFFICACY

The following table from Ms. Mele's statistical review provides comparative data for Climara Pro and other estrogen products approved for the prevention of PMO.

	estradiol arms	estradiol	placebo	Trt Effect
Study A09585	0.0225 mg/day 0.045 mg/day baseline estradiol <5 ≥5 POM >1 to 3 yrs POM >3 to 10 yrs POM >10 yrs	+0.4% +1.7% +2.9% +1.5% +1.1% +1.4% +3.3%	-2.9% - 3.4% - 2.2% - 2.6% - 2.8% - 2.6%	+3.2% +4.9% +6.3% +3.7% +3.7% +4.2% +6.1%
Study A10079	0.045 mg/day+LNG.3 POM >1 to 3 yrs POM >3 to 10 yrs 0.045 mg/day+LNG.4 POM >1 to 3 yrs POM >3 to 10 yrs	+3.8% +4.6% +4.2% +5.2%	-2.6% - 1.6% - 2.6% - 1.6%	+6.4% +6.2% +6.8% +6.8%
Climara	0.05 mg/day (12.5 cm ²) 0.06 mg/day (15 cm ²)	+3.8% +3.4%	-2%	+5.8% +5.4%
Vivelle-Dot	0.0375 mg/day 0.05 mg/day results for all pts combined presented in labeling	+0.25% +0.2	-3%	+3.25% +3.2%
Menostar	0.014 mg/day baseline estradiol <5 ≥5	+3% +3.5% +2.4%	+0.5% +0.3% +0.8%	+2.5% +3.2% +1.6%

The above data indicate that the addition of a progestin to the estradiol in Climara Pro does not attenuate the effects on BMD. In addition, it appears that the BMD effects of similar doses of estrogen found in other transdermal products are comparable to the effects observed with the 0.045 mg of estradiol in Climara Pro.

VII. LABELING

The following three pages provide the labeling as proposed by Berlex.

Clinical Studies - Effects on bone mineral density



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4 Page(s) Withheld

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 Deliberative Process



VIII. CONCLUSION AND REGULATORY RECOMMENDATION

Berlex has provided sufficient evidence to conclude that the 0.045 mg dose of transdermal estradiol is effective and safe for the prevention of PMO. No unexpected safety concerns emerged during review of the submitted data.

The Division's proposed labeling is quite different from the language originally submitted by Berlex. I believe our proposed language is consistent with the labeling of other estrogen products approved for the prevention of PMO.

Contingent upon finalization of labeling, I recommend that this supplemental NDA be approved.

Eric Colman, MD

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/s/

Eric Colman
11/21/2005 07:57:13 AM
MEDICAL OFFICER

David Orloff
11/21/2005 05:09:08 PM
MEDICAL OFFICER
Concur. This will serve as the divisional memo for
this type 6 NDA. Approve.

MEMORANDUM

To: NDA 21-885 (N000-BL)

Through: Eric Colman, MD
Team Leader, HFD-510

From: Brenda S. Gierhart, MD
Medical Officer, HFD-510

Date: November 17, 2005

Re: MO Review of Revised Sponsor Proposed Labeling
Letter date: August 19, 2005
Stamp date: August 22, 2005
Climara Pro® (estradiol/levonorgestrel transdermal system)
Berlex Laboratories, Inc.

Background:

On December 22, 1994, **Climara** (estradiol transdermal system 0.025, 0.0375, 0.05, 0.06, 0.075, and 0.1 mg/24 hours) by Berlex was first approved under NDA 20-375 by HFD-580 for the following indications: treatment of moderate to severe vasomotor symptoms associated with the menopause, treatment of vulvar and vaginal atrophy, and treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. On March 1999, **Climara** (for all the same doses) was approved under the Type 6 NDA 20-994 by HFD-510 for the osteoporosis prevention indication. On June 8, 2004, **Menostar** (estradiol transdermal system 0.014 mg/24 hours) by Berlex was approved under the Type 6 NDA 21-674 by HFD-510 only for the osteoporosis prevention indication.

On November 21, 2003, **Climara Pro** (estradiol/levonorgestrel transdermal system: estradiol 0.045 mg/24 hours, levonorgestrel 0.015 mg/24 hours) was approved under NDA 21-258 by HFD-580 for the treatment of moderate to severe vasomotor symptoms associated with menopause. On February 28, 2005, Berlex submitted the Type 6 NDA 21-885 to obtain the osteoporosis prevention indication for Climara Pro. The labeling submitted with the original Type 6 NDA 21-885 has now been superseded by revised labeling submitted on August 19, 2005. The labeling was revised due to the approval of NDA 21-258 Supplement S-003 **Climara Pro** by HFD-580 on June 22, 2005. NDA 21-258 Supplement S-003 incorporated the WHIMS study results.

Current submission:

The currently submitted labeling is the NDA 21-258 S-003 Climara Pro labeling approved on June 22, 2005 with the addition of osteoporosis prevention information to two sections of the PI and to one section of the PPI. The sponsor highlighted and underlined the osteoporosis prevention information added to the **CLINICAL STUDIES** and **INDICATIONS AND USAGE** sections of the PI and to the **What is Climara Pro used for?** section of the PPI.

The submitted labeling was compared to the latest approved NDA 21-258 Climara Pro and NDA 20-375 Climara labeling (both approved on June 22, 2005) and to the Guidance For Industry: Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for

Health Care Providers and Patient Labeling dated November 2005. The submitted labeling was also compared to other combination estrogen/progestin drug products approved for the osteoporosis prevention indication, i.e., femhrt, Prempro, Premphase, Activella, and Prefest, and to estrogen drug products approved for the osteoporosis prevention indication, i.e. Premarin, Vivelle, Vivelle-Dot, Menostar, and Alora. The Primary Medical Officer Review of NDA 21-885 by Bruce Stadel, MD finalized on 9/14/05 was reviewed, with particular attention to his recommended changes to the labeling.

Recommendation:

1)

2)

3)

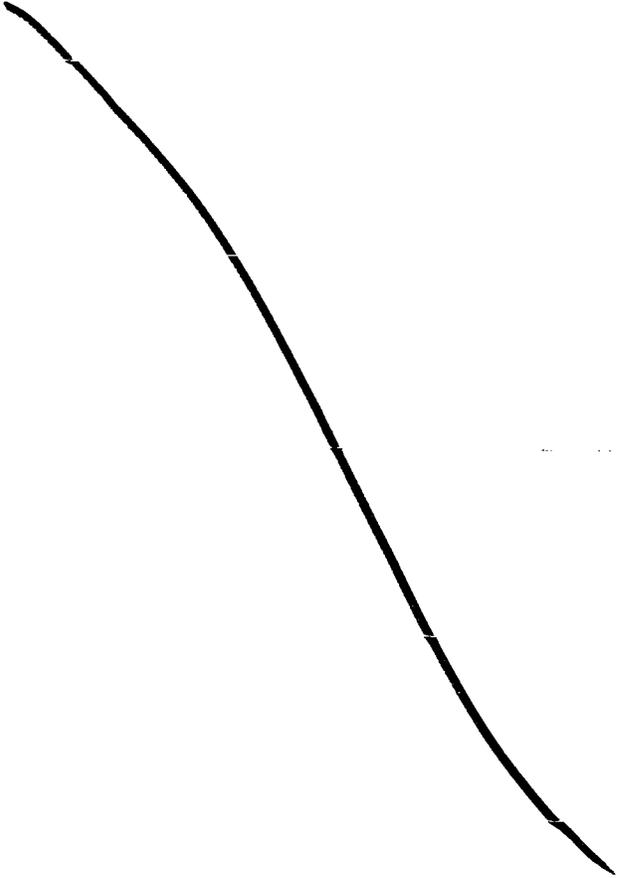
4)

5)

6)

7)

8)



Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling dated November 2005. All changes recommended by HFD-580 have been incorporated into the attached labeling.

- 9) Since the attached labeling is acceptable with all members of the NDA 21-885 review team and with HFD-580, recommend conveying the attached labeling incorporates the above changes to the Sponsor.

cc: HFD-510: D. Orloff, E. Colman, B. Gierhart, and Pat Madara
HFD-580: D. Shames, Phill Price, T. van der Vlugt and G. Lyght

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/s/

Brenda Gierhart
11/17/2005 07:18:59 PM
MEDICAL OFFICER

Clinical Review
Bruce V. Stadel, MD, MPH
NDA 21885
Climara Pro®/17-β estradiol an levonorgestrel, USP

1

CLINICAL REVIEW

Application Type: NDA
Submission Number: 21885
Submission Code: N000

Letter Date: 28 February 2005
Stamp Date: 8 March 2005
PDUFA Goal Date: 1 January 2006

Reviewer Name: Bruce V. Stadel, MD, MPH
Review Completion Date: 13 September 2005

Established Name: 17-β estradiol and levonorgestrel
(Proposed) Trade Name: Climara Pro™
Therapeutic Class: estrogen/progestin
Applicant: Berlex Laboratories, Inc.

Priority Designation: S

Formulation: 17-β estradiol/levonorgestrel transdermal system
Dosing Regimen: 17-β estradiol/levonorgestrel, 0.045/0.015 mg/day
Indication: prevention of postmenopausal osteoporosis
Intended Population: postmenopausal women at risk of osteoporosis

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approve.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

I recommend that consideration be given to a meeting of experts to review the safety of estrogen with progestin versus estrogen without progestin for the prevention of postmenopausal osteoporosis in women with (or without) uteri. For more information, see Appendix 4.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Clinical Program consisted of 2 phase 3 clinical trials, each 104 weeks long with lumbar spine bone mineral density as the primary efficacy variable.

1.3.2 Efficacy

The Pivotal Phase 3 Study demonstrates efficacy for the primary efficacy variable. The mean percent changes from baseline to week 104 were about - 3% for placebo and +1.2% for the dose of estrogen in Climara Pro™ (last observation carried forward). An estrogen-alone transdermal system was studied, with pre-NDA agreement between the Division and Berlex. For more information, See Appendix 1.

1.3.3 Safety

No new information in the studies reviewed. However, recent data suggest that products containing estrogen with progestin may do more harm than products containing estrogen without progestin when used by postmenopausal women with (or without) uteri. See Appendix 4 for more information.

1.3.4 Dosing Regimen and Administration

The dosing regimen and route of administration are daily application of transdermal system containing 17-β estradiol/levonorgestrel 0.045/0.015 mg/day.

1.3.5 Drug-Drug Interactions

No new information in the studies reviewed. Climara Pro™ is an approved drug product. For previous information on drug-drug interactions, see Appendix 3.

1.3.6 Special Populations

None.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Climara Pro™ is an approved drug product, NDA021258. The company is Berlex and the approval date was 21Nov03. The approved indication is: "In women with an intact uterus, Climara Pro™ is indicated for the following: treatment of moderate to severe vasomotor symptoms associated with menopause."

The NDA reviewed here is an efficacy supplement, for the indication of the prevention of postmenopausal osteoporosis.

2.2 Currently Available Treatment for Indications

Several estrogen-alone and estrogen-progestin drug products are approved for the prevention of postmenopausal osteoporosis. Estrogen-alone products include oral Premarin,® Estrace,® Ogen,® and Ortho-Est,® and 2 transdermal formulations, which are Climara® and Vivelle-Dot.® The estrogen-progestin products include oral Prempro,™ Prophase,® Activella,® Femhrt,® and Ortho-Prefest.™ A range of estrogen-alone and estrogen-progestin doses is available.

2.2 Availability of Proposed Active Ingredient in the United States

The proposed active ingredients, 17-β estradiol and levonorgestrel, are available in the United States.

2.4 Important Issues with Pharmacologically Related Products

The most important harm of adding progestin to estrogen for long-term use is an increased risk of breast cancer.¹⁻⁴ For women with uteri, this harm must be weighed against the benefit of protection against endometrial cancer, and recent data suggest that the breast cancer harm may outweigh the endometrial cancer benefit.⁵ See 8. ADDITIONAL CLINICAL ISSUES for more information.

In addition, orally administered estrogen with added progestin, and estrogen alone to a lesser extent, increase the risk of cardiovascular disease, with varying harms reported for coronary heart disease, stroke, and venous thromboembolic disease.^{1,3,6-8} For the transdermal route, there is a study suggesting that the risk of venous thrombosis may not be increased;⁹ other forms of cardiovascular disease have not been studied.

2.5 Presubmission Regulatory Activity

See Appendix 1 (Minutes of 13Oct04 Pre-NDA Meeting).

2.6 Other Relevant Background Information

None.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Only clinical information was required for this NDA supplement. See attached Appendix 1 (Minutes of 13Oct04 Pre-NDA Meeting). See also Memo by Sheldon Markofsky, PhD.

3.2 Animal Pharmacology/Toxicology

Only clinical information was required for this NDA supplement. See Appendix 1 (Minutes of 13Oct04 Pre-NDA Meeting).

3.3 Biometrics

See review by Joy Mele, MS.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Two Phase 3 clinical trials. I reviewed the information on these RCTs that was in the original NDA submission and sent questions to Berlex where I needed more information. The replies were submitted to the NDA and I put information from them in the review.

Clinical Review

Bruce V. Stadel, MD, MPH

NDA 21885

Climara Pro®/17-β estradiol an levonorgestrel, USP

4.2 Tables of Clinical Studies

Table of All Studies

Report No. (Protocol No.)	Country: Principal Investigator(s) Publication	Start Date (mm/yyyy) Duration of Treatment Completion Status	Study Design Study Phase	Dose Treatment	Number of Subjects Who Received Treatment*	Age Range in Years (Mean) Sex Race	Location of Report Location of Publication Location of CRF Tabulations Location of CRFs
i. INDICATION – PREVENTION OF OSTEOPOROSIS							
1.1 Controlled Clinical Studies With Case Report Forms Available							
A09585 (98041)	United States: Akman S Aloia J Block M Brigham J Carpenter K Chestnut C Drotman S Dunston LK Emkey R Ettinger M Gillie E Gordon S Koltun W Kurtz B Lenthan, Jr J Pappas J Speacer-Smith E Wasatch R Wehle S Woodson G Yankaskas M Zitke T NA	05/1998	Multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3	2.2 mg E2 (transdermal delivery system, 22 cm ²)	45	40-74 (51.1)	1) a09585.pdf 2) NA 3) datatoc.pdf 4) crfloc.pdf
		26 cycles		4.4 mg E2 (transdermal delivery system, 22 cm ²)	44	41-69 (51.2)	
		Completed		Placebo (transdermal patch, 22 cm ²)	61	40-83 (51.8)	
						150 Female: 116 Caucasians 27 Blacks 5 Hispanics 2 Asians	

Report No. (Protocol No.)	Country: Principal Investigator(s) Publication	Start Date (mm/yyyy) Duration of Treatment Completion Status	Study Design Study Phase	Dose Treatment	Number of Subjects Who Received Treatment*	Age Range in Years (Mean) Sex Race	Location of Report Location of Publication Location of CRF Tabulations Location of CRFs
A10079 (12226)	Denmark: Bjarnason N Christiansen C Lawaetz H NA	05/1999	Multicenter, double-blind, double-dummy, randomized, placebo-controlled Phase 3	45 µg E2 – 30 µg LNG (transdermal delivery system, 22 cm ²)	69	47-63 (54.1)	1) a10079.pdf 2) NA 3) NA 4) crfloc.pdf
		26 cycles		45 µg E2 – 40 µg LNG (transdermal delivery system, 30 cm ²)	72	47-63 (55.2)	
		Completed		Placebo (transdermal patch, 22 cm ² and 30 cm ²)	71	50-61 (54.6)	
						212 Female: 211 Caucasians 1 Black	

CRF = case report form; E2 = 17β-estradiol; LNG = levonorgestrel; m = month; NA = not applicable; No. = number; y = year.
*Subjects who received at least 1 dose of study medication.

4.3 Review Strategy

I reviewed the NDA submission, asked questions where needed, read relevant publications, and evaluated the NDA submission in the context of benefits and harms.

4.4 Data Quality and Integrity

I evaluated the NDA submission for completeness, internal consistency, and plausibility, in the context of my background in this area and the published literature. The quality and integrity of the data appear to be satisfactory.

4.5 Compliance with Good Clinical Practices

I reviewed the clinical trials in the NDA submission for compliance with Good Clinical Practices, including compliance regarding informed consent, protocol violations, site-specific issues, and ethical standards. The clinical trials appear to be in compliance.

4.6 Financial Disclosures

Financial disclosure evaluation was based on the NDA. The form used was "Certification: Financial Interests and Arrangements of Clinical Investigators" (OMB No. 0910-0396, expiration date 28Feb06). This form was signed by the Head of Clinical Development at Berlex. This form is appropriate and I see no reason to disagree with the certification.

5. CLINICAL PHARMACOLOGY

By cross-reference to human pharmacokinetic and bioavailability information in NDA 21-258. See also review by Johnny Lau, PhD.

5.1 Pharmacokinetics

See above.

5.2 Pharmacodynamics

The main pharmacodynamic outcome is bone mineral density; see Appendix 2 (Review of Individual Studies).

5.3 Exposure-Response Relationships

See above.

6. INTEGRATED REVIEW OF EFFICACY

No Integrated Review of Efficacy was required for this efficacy supplement, since there is only 1 pivotal phase 3 study (Study Report A09585). See attached Minutes of 13Oct04 Pre-NDA Meeting. For efficacy results of the pivotal phase 3 study, see Appendix 2 (Review of Individual Study Reports).

7. INTEGRATED REVIEW OF SAFETY

Safety results are presented separately for the pivotal phase 3 study (Study Report A09585) and the supportive phase 3 study (Study Report A10079), as agreed between the Division and Berlex. See attached Minutes of 13Oct04 Pre-NDA Meeting. For safety results of the pivotal and supportive phase 3 studies, see Appendix 2 (Review of Individual Study Reports).

7.1 Methods and Findings

Sections 7.1.1-7.1.9 of the Review Template are discussed in the reviews of the pivotal and supportive phase 3 studies. See 7. above.

7.1.10 Immunogenicity

No new information in the studies reviewed.

7.1.11 Human Carcinogenicity

No new information in the studies reviewed.

7.1.12 Special Safety Studies

None.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No new information in the studies reviewed.

7.1.14 Human Reproduction and Pregnancy Data

No new information in the studies reviewed.

7.1.15 Assessment of Effect on Growth

None except for bone mineral density as indicator of bone growth.

7.1.16 Overdose Experience

No new information in the studies reviewed.

7.1.17 Postmarketing Experience

Climara Pro™ is an approved drug product. For information on postmarketing experience, see Appendix 3 (Line-by-Line Labeling Review).

8 ADDITIONAL CLINICAL ISSUES

The most important harm of adding progestin to estrogen for long-term use is an increased risk of breast cancer.¹⁻⁴ For women with uteri, this harm must be weighed against the benefit of protection against endometrial cancer – and recent data suggest that the breast cancer harm may outweigh the endometrial cancer benefit.⁵

The main sources of information about these issues are the Women's Health Initiative randomized clinical trials of estrogen plus progestin (EP) and estrogen-alone (E-alone), and the Million Women Study, an observational cohort study which investigated the various EP and E-alone hormone replacement therapy (HRT) products that were used by the participants.

8.1 Women's Health Initiative (United States)

In the EP trial, with a mean follow-up of 5.6 years, there was a statistically significant increase in breast cancer, for EP versus placebo.¹⁻² – whereas, in the E-alone trial, with a mean follow-up of 6.8 years, there was decrease in breast cancer for EP versus placebo that bordered on statistical significance.³ The E-alone result was unexpected and should be interpreted cautiously. See Appendix 4 for more information.

8.2 Million Women Study (United Kingdom)

The most important result in the context of Climara Pro™ is that, for HRT with either continuous or cyclic EP versus E-alone, an increased risk of breast cancer appears to have outweighed a decreased risk of endometrial cancer.^{4,5} See Appendix 4 for more information.

9. OVERALL ASSESSMENT

9.1 Conclusions

The efficacy and safety data that I reviewed in the Climara Pro™ prevention of postmenopausal osteoporosis efficacy supplement meet current standards for approval.

9.2 Recommendation on Regulatory Action

Approve.

9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

I recommend that consideration be given to a meeting of experts to review the safety of estrogen with progestin versus estrogen-alone in postmenopausal osteoporosis in women with (or without) uteri. See Appendix 4 for more information.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Deferred pending decision on approvability.

9.5 Comments to Applicant

Berlex and other companies with drug products containing both estrogen and progestin that are approved or in review for the prevention of postmenopausal osteoporosis indication should be asked to review and comment on the Million Women Study report on endometrial cancer and hormone replacement therapy.⁵

10. REFERENCES

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principle results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-33.
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4. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet*. 2003;362:419-27.
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8. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. The Women's Health Initiative: a randomized trial. *JAMA*. 2003;289:2673-2684.
9. Scarabin P, Oger E, Plu-Bureau G. Differential association of oral and transdermal estrogen with venous thromboembolism risk. *Lancet*. 2003;362:428-32.

APPENDICES

Appendix 1 Minutes of 13Oct04 Pre-NDA Meeting

PRE-MEETING MINUTES

MEETING DATE: October 13, 2004

TIME: 3:00 PM

LOCATION: Teleconference

APPLICATION: PIND 69,721 Climara Pro (estradiol/levonorgestrel transdermal system)

TYPE OF MEETING: Type B; Pre-NDA

MEETING CHAIR: tentative chair: Dr. David Orloff, M.D.; Division Director

MEETING RECORDER: Patricia Madara

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Tentative CDER Participants:

From the Division of Metabolic and Endocrine Drug Products:

Dr. David Orloff, M.D.;	Division Director
Eric Colman, M.D.;	Clinical Team Leader
Bruce Stadel, M.D., MBA;	Medical Officer
Jon T. Sahlroot, Ph.D.;	Biometrics Team Leader
Cynthia Liu, Ph.D.;	Biometrics Reviewer
Karen Davis Bruno, Ph.D.;	Pharmacology/Toxicology Team Leader
Hae Young Ahn, Ph.D.;	Clinical Pharmacology/Biopharmaceutics Team Leader
S.W. Johnny Lau, Ph.D.;	Clinical Pharmacology/Biopharmaceutics Reviewer
Mamta Gautam-Basak, Ph.D.;	Chemistry Team Leader
Pat Madara, M.S.;	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Tentative Berlex Laboratories, Inc. Participants:

Pol Boudes, M.D.,	Director Clinical Operations, Berlex
Sharon Brown,	Director Drug Regulatory Affairs, Berlex

Thomas Holler, Ph.D.,	Project Manager, Berlex
Adel Karara, Ph.D.,	Director Clinical Pharmacology, Berlex
Geoffrey Millington,	Manager, Drug Regulatory Affairs, Berlex
Mino Niknian, Ph.D.,	Director Biostatistics, Berlex
Angelo Secci, M.D.,	Clinician, Female Health Care, Berlex
Klaus Sommer, Ph.D.,	Manager Drug Regulatory Affairs, Berlex
Joeseeph Sonk, Ph.D.,	Vice President Drug Regulatory Affairs, Berlex

Background:

Climara Pro (NDA 21-258) is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause. This NDA resides in the Division of Reproductive and Urologic Drug Products (HFD-580). The sponsor now seeks approval to market Climara Pro for the additional indication of postmenopausal osteoporosis, to allow prescription of the patch for women who need osteoporosis prevention in addition to treatment of vasomotor symptoms. A new (Type 6) NDA would be submitted to the Division of Metabolic and Endocrine Drug Products (HFD-510) for this purpose. The sponsor has requested a pre-NDA meeting to discuss their planned submission of this NDA. In the meeting package, specific questions were submitted for discussion.

Questions and Answers (Bullet Format, Agency answers are in bold):

1. Does the Division concur that provision of nonclinical information for estradiol and levonorgestrel would not be necessary in this supplemental application and that cross reference to this information in NDA 21-258 would be acceptable?
 - **Yes, this is acceptable.**
2. Does the Division concur to cross-reference the human pharmacokinetic and bioavailability information in NDA 21-258 to support the filing of this NDA supplement?
 - **The Division concurs.**
3. Does the Division concur that the pivotal phase 3 study with estradiol only patches (Report A09585) together with the supportive phase 3 study with estradiol/levonorgestrel combination patches (Report A10079) is sufficient for the filing of the supplemental NDA for the indication prevention of postmenopausal osteoporosis for Climara Pro®?

- **Yes, with the following requests:**
 - a. **The efficacy results from the supportive trial should be compared to those from the pivotal trial for strata of women who are similar by baseline characteristics, e.g. race, age, bone mineral density.**
 - b. **The pivotal and supportive trial reports should include an accounting of women contacted for possible enrollment, by race and age, and of women excluded from randomization, by race, age, and reasons. This will provide a basis for comparing the trial populations to the expected marketplace population.**
 - c. **The pivotal and supportive trial reports should include evaluation of efficacy according to endogenous (baseline) estradiol. The cut-off with data in the literature is 5 pg/ml. Other cut-offs may also be considered.**
 - d. **Optimally, the NDA should include information about the effects of Climara Pro® on coagulation/fibrinolysis variables that appear predictive for venous thromboembolic disease based on the published literature.**
4. Does the Division concur that no *in vivo* estradiol release data from the 4.4 mg estradiol only patch used in the pivotal phase 3 study is needed based on: (1) *in vitro* release rates showing estradiol equivalence of this formulation and Climara Pro®, and (2) *in vivo* data showing estradiol bioequivalence between patches with the same estradiol content and varying levonorgestrel content?
- **The sponsor does not need to conduct in vivo bioequivalence study to address the difference between the clinically tested estradiol only patch and Climara Pro™. However, the sponsor should provide the similarity factor (f₂) values for the in vitro release rate comparison for Text Figures 5 and 6 to support the future sNDA submission.**
5. Does the Division concur that no Integrated Summary of Efficacy will be submitted based on the fact that this submission contains only 1 pivotal study (Report A09585), which will be provided as part of this supplement?
- **Yes.**

6. Does the Division concur that the safety results of the pivotal phase 3 study (Report A09585) and the supportive phase 3 study (Report A10079) can be presented separately for each study in the Integrated Summary of Safety?

- Yes.

7. Does the Division concur that the statistical methods utilized for the pivotal study are acceptable?

- **For the supportive study, 1-sided Dunnett's t-test was mentioned. For the pivotal study, only Dunnett's method was mentioned. Please be aware that 2-sided testing is the standard procedure.**

8. Does the Division concur that submission of CMC information to support this supplemental application will be via Type II Drug Master Files?

- We concur.

Minutes Preparer:

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Chair Concurrence:

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Initialed by: ecolman; bstadel; hyahn; kdavisbruno; jtsahlroot; mgautambasak; jlau; cliu

Appendix 2 Review of Individual Study Reports

Appendix 2.1

Review of Pivotal Phase 3 Study (Study Report A09585): "A Multicenter, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Two Doses of Estradiol Given by Continuous Transdermal Administration in the Prevention of Osteoporosis in Postmenopausal Women."

Note: This review is based on the original NDA submission and replies to questions in the submissions dated 29 July 2005, 4 August 2005, and 18 August 2005.

Abbreviations (not shown for units of measurement, e.g., mm for millimeter)

AE = adverse event

SAE = serious adverse event

A-P = anterior-posterior

BMD = bone mineral density in gm/cm²

BP = blood pressure

Climara Pro = Climara Pro™ (17-β estradiol/levonorgestrel transdermal system)

CPMP = Committee on Proprietary Medicinal Products,
European Medicines Evaluation Agency

DEXA = dual energy x-ray absorptiometry

E = 17β estradiol

E 2.2 = 2.2 mg E2-alone transdermal system,
delivering 17β estradiol 0.0225 mcg per day

E 4.4 = 4.4 mg E-2alone transdermal system,
delivering 17β estradiol 0.045 mcg per day

FSH = follicle stimulating hormone

ITT = intent-to-treat

L = lumbar

LNG = levonorgestrel

Mercury= Hg

RCT = randomized clinical trial

vs. = versus

Note: (1) The main review issues are discussed under the **Reviewer Comment** headings; (2) For the NDA supplement being reviewed, the Division agreed to accept efficacy data for E-alone given by the same transdermal system in place of efficacy data for Climara Pro. See attached Minutes of 13Oct04 Pre-NDA Meeting. The doses of E/LNG in Climara-Pro are 4.40 mg/1.39 mg. The E-alone transdermal systems studied were E 2.2 and E 4.4.

1. Objectives

The objective of this RCT was to evaluate the efficacy of E 2.2 and E 4.4 vs. placebo, for the prevention of osteoporosis in postmenopausal women. The primary efficacy variable was the percent change from baseline in BMD of the lumbar spine (A-P view, L2-L4). The secondary efficacy variables were percent changes from baseline in BMD of the non-dominant radius (midshaft) and total hip (non-dominant side); proportions of women with no loss from baseline of BMD at the lumbar spine and total hip (i.e., percent change ≥ 0); and actual changes from screening in biochemical markers of bone metabolism (serum osteocalcin, serum bone-specific alkaline phosphatase, and the deoxypyridinoline/creatinine ratio).

Safety was also evaluated, in terms of AEs, laboratory tests, vital signs, physical examinations (including pelvic examinations), cervical cytology smears, and mammography. However the safety of E-alone is of limited relevance to this NDA review, whereas the Supporting Phase 3 Study of E/LNG is directly relevant. (Study Report a10079).

2. Patient Population

2.1 Geography and Calendar Time

Patients were recruited at 19 centers in the United States, located in: Mineola, NY, Nashville TN, Phoenix AZ, Seattle WA, Wyomissing PA, Baltimore MD, San Diego CA, Tacoma WA, Stuart FL, Lexington KY, Savannah GA, Atlanta GA, Ft. Meyers FL (2 centers), Decatur GA, St. Petersburg FL, Charlotte NC, Santa Rosa CA, and Honolulu HI. The RCT was conducted from 19May98 to 01Feb02.

2.2 Inclusion and Exclusion Criteria

In the discussion below, "previously" or "previous" means before screening or baseline, whichever applies. The information discussed was obtained by history and/or examination at screening or baseline, and judgments about it were generally made by the investigators.

Inclusion Criteria. Female; uterus removed; ≥ 45 years of age; evidence of ovarian failure (amenorrhea, vasomotor symptoms, etc.) at least 1 and less than 5 years previously with serum FSH >40 mIU/mL and serum E <20 pg/mL, or surgical menopause with bilateral oophorectomy within previous 2 months; lumbar spine BMD T-score above -2.5 (A-P view, L2-L4) by DEXA (e.g., Hologic® ≥ 0.81 g/cm² or Lunar® ≥ 0.9 g/cm²); fasting serum cholesterol ≤ 300 mg/dL, triglycerides ≤ 300 mg/dL, or glucose ≤ 140 mg/dL; and signed informed consent.

Exclusion Criteria. Known or suspected bone disease (excluding osteoporosis); lumbar spine BMD T-score below -2.5 (A-P view, L2-L4) by DEXA (Hologic® <0.81 g/cm² or Lunar® <0.9 g/cm²); hypocalcemia or hypercalcemia; vitamin D deficiency; fracture within

previous 6 months; immobilization for at least 2 of the previous 6 months; hot flashes of a frequency or severity requiring hormonal treatment; cervical smear suggestive of low grade squamous intraepithelial lesion or worse; myocardial infarction within previous 6 months or heart disease severe enough for treatment with anti-arrhythmia or anti-angina drugs; thrombophlebitis or thromboembolic disorder within previous 3 years that was unrelated to estrogen treatment or history of these disorders that was related to estrogen treatment; history of stroke or transient ischemic attack; fasting serum cholesterol >300 mg/dL, triglycerides >300 mg/dL, or glucose >140 mg/dL; hypertension; sitting systolic BP \geq 160 mm Hg or diastolic BP \geq 95 at rest; known or suspected malignant or premalignant disease, excluding successfully treated skin cancers other than malignant melanoma; history of sex steroid-dependent malignancy; abnormal findings on gynecological exam that might worsen with hormone treatment; insulin-dependent diabetes mellitus; uncontrolled thyroid disorder; history of clinically significant depression; history of alcohol or drug abuse within previous 2 years; treatment with anticoagulants (heparin or warfarin) or systemic corticosteroids; treatment with estrogen and/or progestin within previous 8 weeks for oral, intrauterine, or intravaginal route, or within previous 6 months for intramuscular route; estrogen implant in place or removed within previous 8 weeks; any disease or condition compromising the function of body systems that could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of study drug; severe systemic disease that could interfere with the conduct of the study or interpretation of the results; significant liver dysfunction or disease; abnormal laboratory value that was considered clinically significant; increased frequency or severity of headaches (including migraine) during previous estrogen treatment; systemic treatment with fluoride, calcitonin, or bisphosphonates; participation in another clinical trial within previous month or treatment with investigational drug within previous 3 months; and any condition precluding ability to obtain all DEXA scans specified in the protocol (e.g., scoliosis, prior lower back surgery, hip prosthesis).

2.3 Withdrawal Criteria

Patients had the right to withdraw at any time, and if a patient did withdraw, the reason was recorded and a final examination done. Patients could be withdrawn for any of the following reasons: treatment failure (lumbar spine_BMD T-score below -2.5 or annualized decrease >6% at 12-month visit or later); occurrence for the first time of migraine headache or increased frequency of unusually severe headache; sudden perceptual disorder (e.g., disturbance of vision or hearing); early symptoms or signs of thrombophlebitis or thromboembolism (e.g., pain or swelling of legs, stabbing pain on breathing, or coughing for no apparent reason); a feeling of pain and tightness in chest; pending surgery (withdrawal 6 weeks before); immobilization (e.g., after an accident); onset of jaundice, hepatitis, generalized itching, epileptic seizure, or a significant rise in BP; all conditions in the exclusion criteria which were also defined as AEs; premature stopping of study drug for any reason (e.g., adverse event, lack of efficacy, protocol deviation); loss to follow-up; death; and withdrawal of consent.

2.4 Screening

A total of 199 patients were screened, of whom 154 (77.4%) were randomized. Of the 45 (22.6%) patients not randomized, the reasons were FSH <40 mIU/mL (n=17), estradiol >20 pg/mL (n=13), withdrew consent (n=7), triglycerides >300 mg/dL (n=6), cholesterol >300 mg/dL (n=6), glucose >140 mg/dL (n=4), elevated thyroid stimulating hormone (n=2), other including BMD outside inclusion criteria, abnormal cervical smear, breast cancer, elevated liver function tests, thromboembolic disorder, patient had uterus, oophorectomy >60 months previously, scoliosis, investigator decision (n=10). The exclusions could be for more than 1 reason. (Submission dated 29 July 2005, page 1)

2.5 Randomization and Follow-up

Patients were randomized by blocks of 7 in a 3:2:2 ratio: 62 to placebo, 45 to E 2.2, and 47 to E 4.4. The modified ITT population included the 150 patients randomized who received at least 1 dose of study drug: 61 in the placebo group, 45 in the E 2.2 group, and 44 in the E 4.4 group. Of these 150 patients, study drug was discontinued prematurely for 76 (50.7%), most often for AEs, which were more frequent in the placebo group than either the E 2.2 group or E 4.4 group. Only 74 (49.3%) patients completed the RCT. See Table 1.

2.6 Patients Analyzed

Efficacy was analyzed for patients in the "Efficacy ITT Population", consisting of those patients in the modified ITT population who did not erroneously switch study drug during the RCT: 61/62 for placebo, 45/45 for E 2.2, and 40/47 for E 4.4. Efficacy was also analyzed for patients meeting a "valid case" definition. Safety was analyzed for patients in the "Safety ITT Population," consisting of all patients in the modified ITT population: 61/62 for placebo, 45/45 for E 2.2, and 44/47 for E 4.4. See Table 1.

Reviewer Comment on 2.6 Patients Analyzed

I asked Berlex to clarify the numbers and footnotes in Table 1. Berlex replied that a total of 154 patients were randomized, of whom 4 were excluded from the Safety ITT Population because they did not receive study drug (1 in the placebo group and 3 in the E 4.4 group). Of the 150 patients in the Safety ITT Population, 4 in the E 4.4 group were excluded because study drug was erroneously changed at ≥ 1 Study Visit. (Submissions dated 29 July 2005, page 2 and 4 August 2005)

3. Calcium and Vitamin D

Based on a dietary calcium survey at baseline, patients received supplements sufficient for their total daily calcium intake to be about 1500 mg; women whose estimated dietary calcium intake was ≥ 1500 mg/day did not receive calcium supplements. Dietary calcium and the need for supplements were re-evaluated after 1 year. Vitamin D supplements were not provided.

The dietary calcium survey instrument was not validated and Vitamin D levels were not measured.

4. RCT Conduct, Data Collection, and Data Analysis

The methods used to conduct the RCT, for the collection of data, and for the analysis were typical for Phase 3 RCTs.

Table 2 shows the schedule of events, by cycles that were 28 days long.

5. Results

The results discussed below are for screening or baseline, whichever applies, and for the Efficacy and Safety ITT Populations at "All Endpoint," which means week 104 with the last observation on study drug carried forward. Other analyses were also done.

5.1 Baseline Characteristics

Table 3 shows baseline characteristics for the placebo, E 2.2, and E 4.4 groups. Patients in the 3 groups were similar by age, race, weight, height, BMD of the lumbar spine (A-P view, L2-L4), non-dominant radius and total hip, and other baseline characteristics. Of the 150 patients in the Safety ITT Population, 86 (57.3%) had undergone bilateral oophorectomy.

5.2 Efficacy

The results for BMD refer to measurement by DEXA of BMD of the lumbar spine (A-P view, L2-L4), total hip (non-dominant side), and radius (mid-shaft). Results are discussed for the Efficacy ITT Population, to the nearest decimal point except where otherwise specified. See statistical review by Dr. Mele for further information.

5.2.1 Main Efficacy Results from Berlex Analyses

BMD of the lumbar spine (A-P view, L2-L4) was the main efficacy variable, and BMD of the total hip (non-dominant side) and non-dominant radius (midshaft) were the most important secondary efficacy variables.

Lumbar Spine. At baseline, mean BMD in g/cm² was 1.1 for placebo, 1.1 for E 2.2, and 1.1 for E 4.4. (Study Report, page 147, to nearest decimal point) At All Endpoint, the mean percent change from baseline was - 3.3% for placebo, + 0.4% for E 2.2, and + 2.1% for E 4.4 (p<0.001 for both E 2.2 and E. 4.4 vs. placebo). See Table 4.

Total Hip. At baseline, mean BMD in g/cm² was 0.9 for placebo, 1.0 for E 2.2, and 1.0 for E 4.4 (Study Report, page 165, to nearest decimal point)

At All Endpoint, the mean percent change from baseline was - 0.8% for placebo, - 0.2% for E 2.2, and + 1.39% for E 4.4 (p=0.202 for E 2.2 vs. placebo; p=0.007 for E 4.4 vs. placebo). See Table 5.

Non-dominant Radius. Neither E 2.2 nor E 4.4 had a meaningful effect on BMD, vs. placebo, at All Endpoint and in other analyses (Study Report, pages 63-66).

Reviewer Comment on 5.2.1 Main Efficacy Results from Berlex Analyses

The All Endpoint results discussed above for the lumbar spine, total hip, and radius are based on 117, 118 and 113, respectively, of the 146 patients in the Efficacy ITT Population. I asked Berlex to clarify accounting for the other patients in the Efficacy ITT Population. Berlex replied that these patients had either no baseline or postbaseline study measurements at the lumbar spine, total hip, or radius.

5.2.2 Efficacy Results from Analyses Requested by Division

In the pre-NDA meeting, the Division said that “the pivotal and supportive trial reports should include evaluation of efficacy according to endogenous (baseline) estradiol. The cut-off with data in the literature is 5 pg/ml. Other cut-offs may also be considered.” See attached Minutes of 13Oct04 Pre-NDA Meeting.

For the pivotal trial, Berlex provided this evaluation only for the percent change from baseline in lumbar spine BMD. These data were not in the Study Report, -- only in the NDA Summary of Risks and Benefits, -- which says “It has been suggested that BMD activity of estrogen treatment in postmenopausal women might depend on the baseline E2 levels.” (NDA Summary of Benefits and Risk, page 7) I think this tentative language is not appropriate, in light of results from the Menostar RCT, which provide strong support for earlier results from observational studies, as discussed in the Medical Officer review of NDA 21647 for Menostar. See Excerpt from Menostar Prescribing Information below.

Excerpt from Menostar™ Prescribing Information

Table 3. Mean percent change in lumbar spine and total hip BMD at 24 months by subgroups of baseline estradiol level (< 5 pg/mL, ≥ 5 pg/mL)						
Baseline estradiol levels	Lumbar spine			Total hip		
	Menostar™	Placebo	Treatment difference	Menostar™	Placebo	Treatment difference
< 5 pg/mL	n = 101 +3.50	n = 97 +0.29	3.21 (p < 0.001)	n = 101 +1.04	n = 96 -1.09	2.13 (p < 0.001)
≥ 5 pg/mL	n = 88 +2.40	n = 89 +0.81	1.59 (p = 0.002)	n = 88 +0.61	n = 89 -0.31	0.92 (p = 0.045)

n = number of patients with data available for each variable

Baseline E2 < 5 pg/ml. At All Endpoint, the mean percent change from baseline in lumbar spine BMD was - 3.3% for placebo, +0.6% for E 2.2, and +3.2% for E 4.4 (p=0.047 for E 2.2 vs. placebo; p=0.004 for E 4.4 vs. placebo). See Table 6.

Baseline E2 > 5 pg/ml. At All Endpoint, the mean percent change from baseline in lumbar spine BMD was -2.2 for placebo, +0.05 for E 2.2, and + 2.1 for E 4.4 (p=0.235 for E 2.2 vs. placebo; p=0.050 for E 4.4 vs. placebo). See Table 7.

Reviewer Comment on 5.2.2 Efficacy Results from Analyses Requested by Division

These results are similar to those seen for Menostar, i.e., E 2.2 and 4.4 increased lumbar spine BMD more in women with baseline E2 \leq 5 pg/ml than in women with higher baseline E2. However, the reliability of these results is limited by the high discontinuation rate in this RCT, and the small numbers of patients in the strata defined by baseline E2.

5.2.3 Other Efficacy Results

BMD-Efficacy ITT Population at Completers Endpoint. In the Efficacy ITT Population, results at the "Completers Endpoint" (final evaluation for patients who were on study drug >644 days) were similar to those at All Endpoint. For lumbar spine and total hip BMD, see Tables 4 and 5, respectively.

BMD-Valid Cases at All Endpoint and Completers Endpoint. Berlex defined "Valid Cases as the 84 (57.5%) of patients in the Efficacy ITT Population who met all inclusion/exclusion criteria, took no prohibited drug, had \geq 75% compliance, completed \geq 13 cycles, and had no major protocol violations). Efficacy for both E 2.2 and E 4.4 vs. placebo was somewhat greater for Valid Cases vs. the whole Efficacy ITT Population. (Study Report, page 63 for lumbar spine BMD, page 69 for total hip BMD, and page 66 for non-dominant radius BMD)

BMD- Subgroups of Patients at All Endpoint. Additional analyses of lumbar spine BMD and total hip BMD were done for the Efficacy ITT Population at All Endpoint, for patients with osteopenia (baseline lumbar spine BMD T-score $>$ -2.5 to \leq -1), recent menopause (onset within previous 3 years), later menopause (onset 3 to 10 years previously), and natural vs. surgical menopause. For lumbar spine BMD, these analyses were no more useful than the analyses requested by the Division for identifying patients who were likely to have experienced greater efficacy than seen in the main Berlex analyses. For total hip BMD, these analyses were not useful in general for identifying such patients. (Study Report, page 83, and NDA Summary of Benefits and Risks, page 7)

Biochemical Markers of Bone Formation and Resorption. The biochemical markers were serum osteocalcin and serum bone-specific alkaline phosphatase for bone formation and urinary deoxypyridinoline/creatinine ratio for bone resorption. The markers of formation were decreased for both E 2.2 and E 4.4 vs. placebo, and the results were statistically significant. The marker of resorption was decreased for both E 2.2 and E 4.4 vs placebo, and the result for E 4.4 was statistically significant. (Study Report, pages 73-82)

Reviewer Comment on 5.2.3 Other Efficacy Results

I asked Berlex to evaluate total hip BMD by baseline E2, to further investigate the value of baseline E2 for patients who were likely to have experienced greater efficacy than seen in the main Berlex analyses. The results did not show that E 2.2 and 4.4 increased total hip BMD more in women with baseline E2 ≤ 5 pg/ml than in women with higher baseline E2. However, the reliability of these results is limited by the high discontinuation rate in this RCT, and the small numbers of patients in the strata defined by baseline E2. (Submission dated 18 August 2005)

5.3 Safety

All safety analyses refer to the Safety ITT Population. See Table 2 for schedule of evaluations.

5.3.1 Extent of Exposure

Table 8 shows the extent of exposure to study drug. The mean (minimum, maximum was 399.9 (10, 742) for placebo, 526.1 (21,757 for E 2.2, and 482.2 (11, 736) for E 4.4.

5.3.2 Adverse Events (AEs)

The discussion below refers to AEs that occurred <30 days after stopping study drug, except where otherwise specified.

5.3.2.1 Deaths

No deaths occurred <30 days after stopping study drug. There were 2 deaths that occurred later: 1 in the placebo group due to complications of intestinal perforation, and 1 in the E 2.2 group due to complications of adenocarcinoma of the rectum. (Study Report, pages 93-94)

5.3.2.2 Serious Adverse Events (SAEs)

There were 2 (3.3%) patients in the placebo group, 4 (8.9%) patients in the E 2.2 group, and no patients in the E 4.4 group with SAEs (including the deaths). Of the 2 patients in the placebo group with SAEs, 1 had arthrosis of the right hip with replacement surgery and 1 had a fracture of the right lateral malleolus related to

falling. There was also 1 other patient in the placebo group who had SAEs >30 days after stopping study drug and died (see above). Of the 4 patients in the E 2.2 group with SAEs, 1 had adenocarcinoma of the rectum and died >30 days after stopping study drug (see above), 1 had hemorrhage related to a sub-epithelial renal pelvic hematoma, 1 had angina pectoris, and 1 had breast cancer. See Table 9.

5.3.2.3 Discontinuation Due to AEs

There were 16 (26.2%) patients in the placebo group, 7 (15.6%) patients in the E 2.2 group, and 7 (15.9%) patients in the E 4.4 group who discontinued study drug due to AEs. This included 5 (8.2%) patients in the placebo group, no patients in the E 2.2 group and no patients in the E 4.4 group who discontinued due to hot flashes. There were no other meaningful differences between the 3 groups. Most of the other discontinuations were due to application site reactions: 7 (11.5%) patients in the placebo group, 5 (11.1%) patients in the E 2.2 group, and 6 (13.6%) patients in the E 4.4 group. See Table 10.

5.3.2.4 Any AE

There were 52 (85.2%) patients in the placebo group, 42 (93.3%) patients in the E 2.2 group, and 41 (93.2%) patients in the E 4.4 group with and AE.

For AEs in ≥5% of patients in any of the 3 groups, there were meaningful differences between the placebo group, E 2.2 group, and E 4.4 group for arthralgia, hot flashes/insomnia, and breast neoplasm/breast pain, and there were high rates in all 3 groups for application site reaction. See Table 11.

Arthralgia. There were 3 (4.9%) patients in the placebo group, 5 (11.1%) patients in the E 2.2 group, and 8 (18.2%) patients in the E 4.4 group with arthralgia. There was a total of 20 arthralgia AE terms, including pain in the knees (n=4), shoulders (n=4), hip (n=5), hands (n=3), and others (n=4). (Submission dated 29 July 2005, page 3, referring to Study Report Appendix 16.2, page 1982)

Hot Flashes/Insomnia. There were 10 (16.4%) patients in the placebo group, 5 (11.1%) patients in the E 2.2 group, and no patients in the E 4.4 group with hot flashes, and there were 4 (6.6%) patients in the placebo group, no patients in the E 2.2 group, and no patients in the E 4.4 group with insomnia.

Breast neoplasm/Breast Pain. There were no patients in the placebo group, 1 (2.2%) patient in the E 2.2 group, and 4 (8.1%) patients in the E 4.4 group with breast neoplasm, and there were 1 (1.6%) patient in the placebo group, 5 (11.1%) patients in the E 2.2 group, and 4 (9.1%) patients in the E 4.4 group with breast pain. Of the 5 patients with breast neoplasms, 1 patient in the E 2.2 group had breast cancer and 4 patients in the E 4.4 group had mammography or physical examination results for which cancer was not confirmed. (Submission dated 29 July 2005, page 3)

Application Site Reaction. There were 22 (36.1%) patients in the placebo group, 12 (26.7%) patients in the E 2.2 group, and 12 (27.3%) patients in the E 4.4 group with application site reactions.

Reviewer Comment on 5.3.2 Adverse Events (AEs)

There was no meaningful differences in deaths or SAEs between the placebo group, E 2.2 group, and E. 4.4 group.

Expected effects of estrogen appear to account for the higher rate of discontinuation for hot flashes in the placebo group vs. the E 2.2 group and E 4.4 group, the higher rates of Any AE called hot flashes or insomnia in the placebo group vs. the E 2.2 group and E 4.4 group, and the higher rates of arthralgia and breast neoplasm/pain in the E 2.2 group and E 4.4 group vs. the placebo group.

For application site reactions, the substantial rates of discontinuation and high rates of Any AE in the placebo group, E 2.2 group, and E 4.4 group suggest that acceptability of the transdermal system may be somewhat limited in postmenopausal women.

5.3.3 Clinical Laboratory Tests

The hematology, chemistry, and lipid variables are listed below. These were reviewed in shift tables for the placebo group, E 2.2 group, and E 4.4 group, with categories of low, normal, and high at baseline and study drug. There were no meaningful differences between the 3 groups. Further analyses of lipids showed some statistically significant differences between the 3 groups, but no consistent pattern was observed. (Study Report, pages 330-534)

Hematology – hemoglobin, hematocrit, red cell count, white cell count, platelet count, and percentages of segmented neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils.

Chemistry – gamma-glutamyl transaminase, aspartate transaminase, alanine transaminase, total bilirubin, lactate dehydrogenase, total protein, albumin, glucose, blood urea nitrogen, creatinine, and uric acid.

Lipids – total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.

No urinalysis results were reported.

5.3.4 Weight and Vital Signs

The variables were weight, systolic BP, diastolic BP, and heart rate. These were reviewed for the placebo group, E 2.2 group, and E 4.4 group in tables of mean, median, minimum, and maximum values, and mean, median, minimum, and maximum changes from baseline.

Weight. There were no meaningful differences between the 3 groups, although some changes from baseline within groups were statistically significant. (Study Report, pages 536-539)

Systolic BP. There were no meaningful differences between the 3 groups, although some changes from baseline within groups were statistically significant. The maximum value at Visit 9/Final Visit was increased (220 mm Hg) in the E 4.4. group vs. the E 2.2 group and placebo group. See Table 12, Systolic BP range for E 4.4. However, the maximum value for the E 4.4 group across Visits 1-8 was between 142-158 mm Hg. (Study Report, pages 540-543)

Diastolic BP. There were no meaningful differences between the placebo and E 2.2 groups, although some changes from baseline within groups were statistically significant. However, the values for the E 4.4 group vs. the placebo group were increased (mean increase=2.6 mm Hg) and these differences were statistically significant. See Table 12. There were also some statistically significant changes from baseline within the E 4.4. group. (Study Report, pages 544-601)

Heart Rate. There were no meaningful differences between the 3 groups, although some changes from baseline within groups were statistically significant. (Study Report, pages 548-551)

5.3.5 Physical Examinations (including Pelvic)

Examinations were done for general appearance, skin, eyes/ears/nose/throat, head and neck, lungs, heart, breasts, abdomen, lymph nodes, musculoskeletal system, neurological system, external genitalia, vagina, cervix, and adenexa. These were reviewed in shift tables for the placebo group, E 2.2 group, and E 4.4 group, with categories of normal, abnormal, and not done at screening and on study drug. There were no meaningful differences between the placebo group, E 2.2 group, and E 4.4 group except for the breasts. (Study Report, pages 552-596)

Breasts. There were no patients with normal results at screening and abnormal results on placebo. In the E 2.2 group, there were 2 (5.3%) patients with normal results at screening and abnormal results at Visit 3, and 1 (2.6%) patient with normal results at screening and abnormal results at Visit 9/Final Visit. In the E 4.4 group, there were 2 (8.3%) patients with normal results at screening and abnormal results at Visit 7, and there were 3 (7.5%) patients with normal results at screening and abnormal results at Visit 9/Final Visit. (Study Report, pages 558, 573, and 588) Of the 8 patients in the E 2.2 or E 4.4 with normal results at screening and abnormal results at Visit 3 through Visit 9/Final Visit, 2 in the E 2.2 group and 2 in the E 4.4 has abnormal physical examination results and the remainder had abnormal mammograms.

5.3.6 Cervical Cytology

Results were reviewed in shift tables for the placebo group, E 2.2 group, and E 4.4 group, with categories of normal, benign, and abnormal at screening and on study drug. There were no meaningful differences between the 3 groups. (Study Report, page 597)

5.3.7 Mammography

Results were reviewed in shift tables for the placebo group, E 2.2 group, and E 4.4 group, with categories of normal, abnormal, and not done at screening and on study drug.

In the placebo group, there were 3 (10.0%) patients with normal results at screening and abnormal results at Visit 5, and there was 1 (1.9%) patient with normal results at screening and abnormal results at Visit 9/Final Visit. In the E 2.2 group, there was 1 (3.3%) patient with normal results at screening and abnormal results at Visit 5, and there were 2 (5.1%) patients with normal results at screening and abnormal results at Visit 9/Final Visit. In the E 4.4 group, there were 3 (10.7%) patients with normal results at screening and abnormal results at Visit 5, and there were 3 (7.7%) patients with normal results at screening and abnormal results at Visit 9/Final Visit. (Study Report, pages 598-600)

For the 1 patient in the E 2.2 group with normal results at screening and abnormal results at Visit 9/Final Visits, the results were "highly suggestive of malignancy," and breast cancer was diagnosed. (Study Report, pages 108-109)

6. Discussion

Efficacy. I think the RCT for E 2.2 and E 4.4 vs. placebo supports efficacy, because: (1) the efficacy of estrogen for the prevention of postmenopausal osteoporosis indication is well-established in general, (2) the results of the RCT for the primary efficacy variable were statistically significant, and (3) the results of the RCT were nearly identical to those for Vivelle-Dot® 0.05 mg/day, which is approved for the prevention of postmenopausal osteoporosis indication.

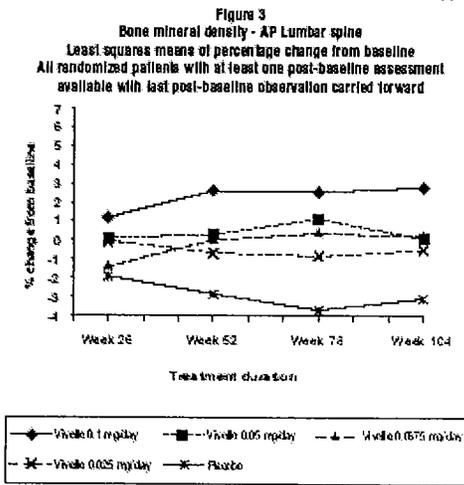
The comparison with Vivelle-Dot® 0.05 mg/day is important because of limitations in the methods of the RCT for E 2.2 and E 4.4, mainly that vitamin D deficiency was determined by medical history only, vitamin D supplements were not given, the dietary calcium survey instrument was not validated, calcium supplements were given only to patients who appeared deficient according to the survey, and withdrawal before the end of the RCT was substantial.

The comparison with Vivelle-Dot® 0.05 mg/day is appropriate because the E 2.2 and E 4.4 transdermal systems studied in the RCT delivered E at 0.0225 mcg/day and 0.045 mcg per day, respectively, and Vivelle-Dot® 0.05 mg/day delivers E at 0.05 mg E/day.

The primary efficacy variable was the percent change from baseline in lumbar spine BMD in the RCTs for E 2.2 and E 4.4, and Vivelle-Dot® 0.05 mg/day.

In the RCT for E2 and E 4.4, the mean percent changes from baseline to week 104 with the last observation on study drug carried forward (All Endpoint) were -3.2 for in the placebo group, -1.2 in the E 2.2 group, and +1.2 in the E 4.4 group (to nearest decimal point). In the Prescribing Information for Vivelle-Dot®, the mean percent changes from baseline to week 104 with the last observation on study drug carried forward are about - 3% for placebo +<1% for Vivelle-Dot® 0.05 mg/day, and +3% for Vivelle-Dot® 0.1 mg/day:

Excerpt from Vivelle-Dot® Prescribing Information



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Safety. There were no unexpected results and the RCT raised no safety concerns.

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Table 1. Patient Disposition (Study Report, page 120)

	Placebo		E2 2.2mg		E2 4.4mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Screened							199	
Randomized †	62		45		47		154	
Safety ITR Population *	61		45		44		150	
Efficacy ITR Population ‡	61		45		40		146	
Completed	27	(44.3)	25	(55.6)	22	(50.0)	74	(49.3)
Discontinuation of Study Medication	34	(55.7)	20	(44.4)	22	(50.0)	76	(50.7)
Averse Events	16	(26.2)	7	(15.6)	7	(15.9)	30	(20.0)
Lack of Efficacy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Protocol Deviation	3	(4.9)	3	(6.7)	7	(15.9)	13	(8.7)
Withdrawal of Consent	2	(3.2)	2	(4.4)	2	(4.7)	6	(4.0)
Other††	3	(4.8)	3	(6.7)	5	(11.1)	11	(7.2)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Subject 3006 & 16004 were originally randomized to Placebo but were reclassified to E2 4.4 mg due to erroneously switching drug during the study.
 ‡ All randomized subjects who received at least 1 dose of study medication.
 § All randomized subjects who received at least 1 dose of study medication & did not erroneously switch drug during the study.
 ¶ Excludes subjects 3004, 3006, 16004 & 16005.
 †† Other includes lost to follow-up subjects.

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Table 2. RCT Schedule of Events (Study Report, page 32)

Study Evaluations	Screening ^a		Baseline	Visit 1 Cycle 1	Visit 2 Cycle 3	Visit 3 Cycle 6	Visit 4 Cycle 9	Visit 5 Cycle 13	Visit 6 Cycle 16	Visit 7 Cycle 19	Visit 8 Cycle 22	Visit 9 ^b Cycle 26
	X	X	X	X	X	X	X	X	X	X	X	X
Medical and Medication History	X											
Physical Exam including Pelvic/Vaginal Pap smear and Breast Exam	X											
Vital Signs and Weight	X			X	X	X	X	X	X	X	X	X
Mammography ^c	X			X	X	X	X	X	X	X	X	X
X-ray of Spine ^d	X											
Bone Densitometry of Spine (A-P view, L2 - L4), Total hip, Mid-Shaft of Radius (DEXA scans), General Laboratory Studies and Lipid Profile			X			X		X		X		X
Follicle-stimulating and Thyroid-stimulating hormones, and Estradiol levels			X									
Serum Calcocalcin, Serum Bone-Specific Alkaline Phosphatase, Urinary DeoxyPyridinoline Crosslinks			X			X		X		X		X
Calcium Survey			X					X				
Adverse Event/Injuries				X	X	X	X	X	X	X	X	X
Record Concomitant Medications			X	X	X	X	X	X	X	X	X	X
Medication Dispensed/Returned ^e			X	X	X	X	X	X	X	X	X	X

L2 - L4 = second through fourth lumbar vertebrae; DEXA = Dual Energy X-ray Absorptiometry

^a Screening could not take place until the subject had been off estrogen replacement therapy for at least 2 months. There was to be no more than 4 weeks between screening and baseline.

^b If the subject was prematurely withdrawn from the study, all the evaluations described under Visit 9 were to be performed at the final visit.

^c A negative mammography had been reported 6 months prior to visit, (provided the report is available) it was not necessary to be repeated at screening. Mammogram at Visit 5 is optional in women <55 years old.

^d The X-ray of spine was to be repeated at any visit, if a fracture was suspected.

^e Medication could be dispensed only after entry criteria had been satisfied.

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Table 3. Baseline Characteristics (Study Report, pages 53-54)

Category	Treatment Group			P value ^a
	Placebo (N = 61)	E ₂ 2.2 mg (N = 45)	E ₂ 4.4 mg (N = 44)	
Age (y)				0.855
N	61	45	44	
Mean (SD)	51.8 (7.81)	51.1 (6.41)	51.2 (6.32)	
Median	51.0	51.0	51.0	
Range	40 — 83	40 — 74	41 — 89	
Race (n [%])				0.148
n	61	45	44	
Caucasian	48 (78.7%)	37 (82.2%)	31 (70.5%)	
Black	8 (13.1%)	8 (17.8%)	11 (25.0%)	
Hispanic	3 (4.9%)	0 (0.0%)	2 (4.5%)	
Asian	2 (3.3%)	0 (0.0%)	0 (0.0%)	
Years Since Menopause				0.515
n	61	45	44	
Mean (SD)	10.6 (11.18)	11.1 (10.53)	9.0 (7.98)	
Median	4.5	4.7	5.1	
Range	0 — 81	0 — 35	1 — 27	
Oophorectomy				0.811
n	61	45	44	
Yes (unilateral)	8	8	8	
Yes (bilateral)	35	25	26	
No	20	12	12	
E ₂ (pg/mL)				0.265
n	45	35	34	
Mean (SD)	7.32 (5.315)	9.46 (12.478)	7.34 (5.465)	
Median	6.30	6.20	5.50	
Range	1.4 — 25.7	1.6 — 75.6	1.5 — 24.8	
Weight (lb)				0.989
n	61	45	44	
Mean (SD)	167.9 (38.00)	169.5 (33.51)	168.1 (31.59)	
Median	158.5	167.3	163.3	
Range	89 — 256	114 — 261	110 — 251	
Height (in)				0.255
n	61	45	44	
Mean (SD)	63.9 (2.32)	63.8 (2.60)	64.5 (2.33)	
Median	64.0	64.0	64.0	
Range	59 — 69	58 — 70	60 — 71	

N = total number of subjects randomized to the study and known to have taken at least 1 dose of drug.
 BMD = bone mineral density; FSH = follicle stimulating hormone; L2 - L4 = second through fourth lumbar vertebrae;
 n = number of subjects with values for this parameter; SD = standard deviation; TMT = treatment.

^a Treatment effect P value was obtained from the following ANOVA model: Y = TMT CENTER or generalized Cochran-Mantel-Haenszel test stratified for center.

^b Obtained from [redacted] data transfer.

Continued on next page.

Table 3 continued.

Category	Treatment Group			P value ^a
	Placebo (N = 61)	E ₂ 2.2 mg (N = 45)	E ₂ 4.4 mg (N = 44)	
BMD T-Score^b				0.690
n	60	42	43	
Mean (SD)	-0.2335 (1.35299)	0.0751 (1.48974)	-0.0658 (1.29804)	
Median	-0.0679	-0.2105	-0.4058	
Range	-2.221 — 3.911	-2.289 — 3.453	-2.759 — 3.728	
BMD Spine (A-P view, L2 - L4) (g/cm³)				0.535
n	60	42	43	
Mean (SD)	1.0944 (0.17124)	1.1442 (0.19164)	1.1277 (0.17541)	
Median	1.0668	1.1000	1.0903	
Range	0.845 — 1.651	0.857 — 1.597	0.846 — 1.629	
BMD Mid-shaft (1/3) Radius (g/cm³)				0.394
n	60	39	42	
Mean (SD)	0.8740 (0.06402)	0.8493 (0.27914)	0.8948 (0.05928)	
Median	0.8800	0.8920	0.8880	
Range	0.487 — 0.785	-1.000 — 0.824	0.570 — 0.831	
BMD Total Hip (g/cm³)				0.655
N	60	41	43	
Mean (SD)	0.9329 (0.14088)	0.9876 (0.14906)	0.9590 (0.14028)	
Median	0.9300	0.9530	0.9250	
Range	0.534 — 1.184	0.723 — 1.263	0.718 — 1.233	
Serum Osteocalcin (ng/mL)				0.320
N	61	45	43	
Mean (SD)	21.41 (8.253)	20.08 (7.040)	22.57 (8.908)	
Median	19.40	19.90	21.50	
Range	9.4 — 47.2	7.4 — 34.4	7.1 — 39.1	
Serum Bone-Specific Alkaline Phosphatase (ng/mL)				0.621
n	60	45	43	
Mean (SD)	10.69 (7.188)	9.77 (8.305)	10.22 (4.425)	
Median	8.05	8.00	9.00	
Range	3.2 — 33.7	2.3 — 34.1	3.6 — 18.7	
Deoxypyridinoline/Creatinine Ratio				0.756
N	60	44	43	
Mean (SD)	0.0744 (0.02884)	0.0790 (0.03770)	0.0753 (0.02637)	
Median	0.0710	0.0700	0.0720	
Range	0.008 — 0.149	0.011 — 0.225	0.039 — 0.160	

N = total number of subjects randomized to the study and known to have taken at least 1 dose of drug.
BMD = bone mineral density; FSH = follicle stimulating hormone; L2 - L4 = second through fourth lumbar vertebrae;
n = number of subjects with values for this parameter; SD = standard deviation; TMT = treatment.

^a Treatment effect P value was obtained from the following ANOVA model: Y = TMT CENTER or generalized Cochran-Mantel-Haenszel^c test stratified for center.

^b Obtained from [REDACTED] data transfer.

Table 4. Percent Change from Baseline, Lumbar Spine BMD (A-P view, L2-L4)
 (Study Report, page 61)

Treatment Group	Statistics	Time Period						All Endpoint*	Completers Endpoint†
		Visit 3/ Cycle 6	Visit 5/ Cycle 13	Visit 7/ Cycle 19	Visit 9/ Cycle 26				
E ₂ 2.2 mg (N = 61)	N	40	32	27	25	45	27		
	Mean Change (SD)	-1.3131 (2.94681)	-1.8677 (3.69481)	-1.9504 (4.46297)	-3.5627 (4.12045)	-2.8403 (3.81534)	-3.2816 (4.36317)		
	Median	-1.1654	-2.4282	-1.6626	-4.1925	-3.1586	-4.1825		
	Min - Max	-8.310 - 4.421	-8.312 - 7.188	-10.471 - 6.006	-8.268 - 3.728	-8.268 - 5.747	-9.268 - 5.747		
E ₂ 2.2 mg (N = 45)	N	36	28	26	21	38	25		
	Mean Change (SD)	0.5769 (3.27528)	1.1602 (3.49819)	0.7483 (3.75906)	0.2279 (4.23356)	0.4241 (4.24893)	0.3932 (4.28467)		
	Median	0.4175	-0.2894	0.4532	-1.0641	-1.1729	-1.0641		
	Min - Max	-6.668 - 8.200	-4.186 - 9.013	-4.168 - 10.434	-7.581 - 8.977	-7.581 - 9.061	-7.581 - 8.987		
E ₂ 4.4 mg (N = 40)	N	33	25	19	18	34	21		
	Mean Change (SD)	0.6317 (3.31440)	1.7425 (3.71140)	3.2711 (4.71509)	2.4395 (5.31815)	2.0607 (4.22029)	2.5943 (5.05050)		
	Median	0.6452	0.7022	2.8933	1.3524	1.2358	1.8539		
	Min - Max	-4.298 - 12.308	-2.890 - 14.110	-3.323 - 16.735	-4.420 - 16.343	-4.420 - 16.343	-4.420 - 16.343		
	P value ^e	0.903 *	<0.001 *	<0.001 *	<0.001 *	<0.001 *	<0.001 *		
	Overall P value ^d	0.003 *	<0.001 *	<0.001 *	<0.001 *	<0.001 *	<0.001 *		

E₂ = 17β-estradiol; max = maximum; min = minimum; N = total number of subjects; SD = standard deviation; TMT = treatment.
 * Number of subjects may vary from visit to visit due to missing data.
 † All Endpoint is the final evaluation on study medication carried forward.
 ‡ Completers Endpoint is the final evaluation of subjects who have been on drug for more than 644 days.
 § P values are for comparisons of each dose against placebo. P values were adjusted by Dunnett's method in the ANCOVA model. Y = TMT CENTER BASE.
 ¶ Overall treatment P value obtained from the following ANCOVA model with baseline covariate: Y = TMT CENTER BASE.
 †† P < 0.05

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Table 5. Percent Change from Baseline, Total Hip BMD
 (Study Report, page 67)

Treatment Group	Statistics	Time Period						All Endpoint ¹	Completers Endpoint ²
		Visit 3/ Cycle 6	Visit 5/ Cycle 13	Visit 7/ Cycle 19	Visit 9/ Cycle 26				
Placebo (N = 61)	n	40	32	26	23	46	27		
	Mean Change (SD)	-1.0826 (2.37776)	-0.4484 (5.65231)	-0.0166 (6.56741)	-0.1269 (7.03077)	-0.8536 (5.27806)	-0.0839 (6.49132)		
	Median	-0.8527	-1.4533	-1.5369	-1.8960	-1.3098	-1.2291		
	Min - Max	-7.018 - 3.487	-5.578 - 23.013	-6.684 - 25.158	-6.174 - 26.996	-6.174 - 26.996	-6.174 - 26.996		
E ₂ 2.2 mg (N = 45)	n	35	27	28	21	38	25		
	Mean Change (SD)	0.6800 (3.49421)	0.5318 (3.46615)	0.6531 (3.45661)	-0.9476 (2.74293)	-0.1929 (3.50692)	-0.7207 (2.75839)		
	Median	0.0867	0.0662	0.7509	-0.8185	-0.1324	-0.4193		
	Min - Max	-5.686 - 15.255	-4.671 - 11.926	-4.623 - 13.775	-6.533 - 3.717	-6.533 - 13.775	-6.533 - 3.717		
E ₂ 4.4 mg (N = 40)	n	34	23	18	16	34	21		
	Mean Change (SD)	0.9869 (3.54799)	1.3297 (4.21925)	1.8294 (5.46876)	2.5690 (5.50829)	1.9927 (4.32491)	2.2149 (5.19853)		
	Median	0.1432	0.5885	0.7105	1.6029	1.1856	1.2931		
	Min - Max	-3.410 - 17.745	-3.532 - 18.357	-2.985 - 22.155	-3.410 - 22.768	-3.410 - 22.768	-3.410 - 22.768		
	P value ³	0.002 *	0.058	0.134	0.113	0.001 *	0.046 *		
	Overall P value ⁴	<0.001 *	0.030	0.116	0.174	0.007 *	0.078		

E₂ = 17β-estradiol; max = maximum; min = minimum; N = total number of subjects; SD = standard deviation; TMT = treatment.
 Number of subjects may vary from visit to visit due to missing data.
 1 All Endpoint is the final evaluation on study medication carried forward.
 2 Completers Endpoint is the final evaluation of subjects who have been on drug for more than 644 days.
 3 P values are for comparison of each dose against placebo. P values were adjusted by Dunnett's method in the ANCOVA model. Y = TMT CENTER BASE.
 4 Overall treatment P value obtained from the following ANCOVA model with baseline covariate: Y = TMT CENTER BASE.
 * P<0.05

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Clinical Review
 Bruce V. Stadel, MD, MPH
 NDA 21885
 Climara Pro®/17-β estradiol an levonorgestrel, USP

Table 6. E2 < 5 pg/ml: Percent Change from Baseline, Lumbar Spine BMD (A-P view, L2-L4) (NDA Summary of Risks and Benefits, Appendix, page 14)

Treatment group	Statistics	Visit/ Cycle 6 (31-365 Days)	Visit/ Cycle 13 (266-453 Days)	Visit/ Cycle 19 (451-644 Days)	Visit/ Cycle 26 (626-845 Days)	ALL Endpoint	Comparators Endpoint
Placebo (N= 17)	n	12	10	9	7	13	8
	MEAN	-1.3817	-2.5369	-1.9249	-4.7822	-3.2593	-3.6723
	SD	1.1654	4.0856	2.5077	4.1895	3.3289	4.1925
	MINIMUM	1.86658	4.24936	4.00598	3.54247	4.19481	4.69246
	MAXIMUM	-5.4893	-5.979	-7.850	-8.288	-9.789	-8.288
E2 2.2mg (N= 14)	n	11	7	7	6	11	7
	MEAN	-0.1554	1.7553	0.3352	0.9825	0.5701	1.9245
	SD	0.1335	3.6204	0.7448	1.0285	1.2835	3.4155
	MINIMUM	2.68301	2.88845	2.81678	4.10487	3.94307	4.11413
	MAXIMUM	-5.010	-2.211	-3.322	-4.105	-4.105	-4.105
E2 4.4mg (N= 13)	n	9	9	7	7	10	8
	MEAN	0.3405	2.1000	2.8703	3.0625	3.2008	3.5994
	SD	0.4575	1.7185	1.5712	2.5191	2.6982	2.6982
	MINIMUM	2.49405	3.11305	3.77668	4.84535	4.14269	4.65208
	MAXIMUM	-2.404	-2.464	-1.151	-1.013	-1.013	-1.013
Overall	P-value (1)	0.192	0.032 *	0.014 *	0.092	0.002 *	0.025 *
	P-value (2)	0.261	0.045 *	0.025 *	0.122	0.004 *	0.038 *

(1) P-values are from comparisons of each dose against placebo
 (2) Overall treatment p-values corrected for the following model with baseline covariates: Y = TREATMENT BASE (1, 2, 3)
 Number of subject carry over from visit to visit due to missing data
 All Endpoint is the final evaluation on study medication carried forward
 Comparators Endpoint is the final evaluation of subjects who have been on drug for more than 644 days

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Table 7. E2 > 5 pg/ml: Percent Change from Baseline, Lumbar Spine BMD (A-P view, L2-L4) (NDA Summary of Risks and Benefits, Appendix, page 15)

Treatment group	Statistics	Visit 2 Cycle 2 (31-265 Days)	Visit 13 Cycle 13 (266-430 Days)	Visit 19 Cycle 19 (451-544 Days)	Visit 26 Cycle 26 (525-645 Days)	ALL Endpoint	Comparator's Endpoint
Placebo (N= 24)	n	19	13	12	12	20	12
	MEAN	-0.4831	-1.1538	-2.2269	-2.8037	-2.2012	-2.8037
	SD	0.3156	0.3459	0.41264	0.40039	0.4632	0.40039
	MINIMUM	3.40962	3.46127	4.81755	4.74485	4.26230	4.74465
	MAXIMUM	-8.310	-6.684	-10.471	-8.587	-8.987	-8.987
E2 2.2mg (N= 21)	n	17	14	13	10	10	12
	MEAN	1.3439	0.9675	0.8916	-0.2869	0.0464	-0.7534
	SD	0.4092	0.3869	0.5204	0.7632	1.3819	1.3813
	MINIMUM	4.62365	4.13866	4.43428	5.04626	4.88836	4.71717
	MAXIMUM	-6.863	-4.186	-4.128	-7.881	-7.881	-7.091
E2 4.4mg (N= 17)	n	16	11	9	8	10	9
	MEAN	1.1142	2.3674	4.2576	2.6047	2.0555	3.0254
	SD	0.3109	0.3035	0.6722	0.5739	0.8259	1.0539
	MINIMUM	4.02895	4.40258	5.42385	5.50145	4.86585	5.21115
	MAXIMUM	-4.284	-2.680	-0.193	-4.420	-4.420	-4.420
Overall	P-value (1)	0.357	0.499	0.090	0.251	0.050 *	0.343
	P-value (2)	0.246	0.549	0.131	0.341	0.078	0.270

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(1) P-values are from comparisons of each dose against placebo
 P-values were adjusted by the Dunnett's method
 (2) Overall treatment p-value obtained from the following model with baseline covariate: Y = TREATMENT CENTER BASE (*1 P<.05)
 Number of subject vary from visit to visit due to missing data
 All endpoints is the final evaluation on study medication carried forward
 Complete's endpoint is the final evaluation of subjects who have been on drug for more than 644 days

Table 8. Extent of Exposure to Study Drug (Study Report, page 87)

Category	Treatment Group		
	Placebo	E, 2.2 mg	E, 4.4 mg
Number of subjects*	60	45	43
Mean (SD)	392.9 (314.25)	526.1 (263.21)	482.2 (291.34)
Median	368.0	721.0	718.0
Minimum	10	21	11
Maximum	747	757	736

SD = standard deviation.

Duration of treatment was defined as the time from the first patch applied to the last dose date of medication.

* Study drug stop dates were not available for 2 subjects who were excluded from this analysis (1 subject each, placebo and E, 4.4 mg treatment groups).

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Table 9. Serious Adverse Events (SAEs) (Study Report, page 248)

Body System/Adverse Event	Placebo (N = 61) n (%)	E2 2.2mg (N = 45) n (%)	E2 4.4mg (N = 44) n (%)	Total (N = 150) n (%)
Number of subjects who reported at least 1 adverse event	2 (3.3)	4 (8.9)	0 (0.0)	6 (4.0)
BODY AS A WHOLE				
SURGERY	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
Total - BODY AS A WHOLE	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
CARDIOVASCULAR				
ANGINA PECTORIS	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
HEMORRHAGE	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
Total - CARDIOVASCULAR	0 (0.0)	2 (4.4)	0 (0.0)	2 (1.3)
DIGESTIVE				
GASTROINTESTINAL CARCINOMA	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
Total - DIGESTIVE	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
MUSCULOSKELETAL				
ARTHRITIS	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
BONE FRACTURE (NOT SPONTANEOUS)	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
Total - MUSCULOSKELETAL	2 (3.3)	0 (0.0)	0 (0.0)	2 (1.3)
SKIN				
BREAST CARCINOMA	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
BREAST NEOPLASIA	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)

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Table 10. Discontinuations Due To AEs (Study Report, 256)

Body System/Adverse Event	Placebo (N = 61) n (%)	E2 2.2mg (N = 45) n (%)	E2 4.4mg (N = 44) n (%)	Total (N = 150) n (%)
Number of subjects who reported at least 1 adverse event	16 (26.2)	7 (15.6)	7 (15.9)	30 (20.0)
BODY AS A WHOLE				
INFECTION	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
PAIN	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
Total - BODY AS A WHOLE	1 (1.6)	1 (2.2)	0 (0.0)	2 (1.3)
CARDIOVASCULAR				
HYPERTENSION	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
Total - CARDIOVASCULAR	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
DIGESTIVE				
GASTROINTESTINAL CARCINOMA	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.7)
GASTROINTESTINAL DISORDER	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
NAUSEA	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
Total - DIGESTIVE	2 (3.3)	1 (2.2)	0 (0.0)	3 (2.0)
NERVOUS SYSTEM				
EMOTIONAL LABILITY	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
HOT FLASHES	5 (8.2)	0 (0.0)	0 (0.0)	5 (3.3)
Total - NERVOUS SYSTEM	6 (9.8)	0 (0.0)	0 (0.0)	6 (4.0)
SKIN				
ALOPECIA	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
APPLICATION SITE REACTION	7 (11.5)	5 (11.1)	4 (9.1)	16 (10.7)
BREAST ENLARGEMENT	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
Total - SKIN	7 (11.5)	5 (11.1)	6 (13.6)	18 (12.0)

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Table 11. Any AE Reported for ≥5% of Patients in Any Group
 (Study Report, pages 89-90)

Body System/ Adverse Event	Treatment Group			Total (N = 150) n (%)
	Placebo (N = 61) n (%)	E ₂ 2.2 mg (N = 45) n (%)	E ₂ 4.4 mg (N = 44) n (%)	
Number of subjects who reported at least one AE*	52 (85.2)	42 (93.3)	41 (93.2)	135 (90.0)
Body as a Whole				
Accidental Injury	2 (3.3)	7 (15.6)	3 (6.8)	12 (8.0)
Allergic Reaction	4 (6.6)	0 (0.0)	1 (2.3)	5 (3.3)
Asthenia	1 (1.6)	2 (4.4)	3 (6.8)	6 (4.0)
Back Pain	5 (8.2)	3 (6.7)	6 (13.6)	14 (9.3)
Flu Syndrome	12 (19.7)	3 (6.7)	5 (11.4)	20 (13.3)
Infection	5 (8.2)	3 (6.7)	4 (9.1)	12 (8.0)
Pain	9 (14.8)	6 (13.3)	6 (13.6)	21 (14.0)
Surgery	0 (0.0)	3 (6.7)	0 (0.0)	3 (2.0)
Digestive				
Constipation	4 (6.6)	1 (2.2)	2 (4.5)	7 (4.7)
Flatulence	1 (1.6)	3 (6.7)	1 (2.3)	5 (3.3)
Gastrointestinal Disorder	6 (9.8)	4 (8.9)	0 (0.0)	10 (6.7)
Nausea	7 (11.5)	3 (6.7)	1 (2.3)	11 (7.3)
Metabolic and Nutrition				
Edema	2 (3.3)	4 (8.9)	4 (9.1)	10 (6.7)
Musculoskeletal				
Arthralgia	3 (4.9)	5 (11.1)	3 (6.8)	16 (10.7)
Nervous System				
Depression	4 (6.6)	1 (2.2)	1 (2.3)	6 (4.0)
Hot Flashes	10 (16.4)	5 (11.1)	0 (0.0)	15 (10.0)
Insomnia	4 (6.6)	0 (0.0)	0 (0.0)	4 (2.7)
Respiratory				
Bronchitis	0 (0.0)	4 (8.9)	0 (0.0)	4 (2.7)
Sinusitis	8 (13.1)	2 (4.4)	5 (11.4)	15 (10.0)
Upper Respiratory Infection	10 (16.4)	10 (22.2)	4 (9.1)	24 (16.0)
Skin				
Application Site Reaction	22 (36.1)	12 (26.7)	12 (27.3)	46 (30.7)
Breast Neoplasm	0 (0.0)	1 (2.2)	4 (9.1)	5 (3.3)
Breast Pain	1 (1.6)	5 (11.1)	4 (9.1)	10 (6.7)
Pruritus	0 (0.0)	3 (6.7)	1 (2.3)	4 (2.7)
Special Senses				
Otitis Media	0 (0.0)	0 (0.0)	3 (6.8)	3 (2.0)
Urogenital				
Urinary Incontinence	0 (0.0)	0 (0.0)	3 (6.8)	3 (2.0)
Urinary Tract Infection	1 (1.6)	5 (11.1)	1 (2.3)	7 (4.7)
Vaginitis	2 (3.3)	3 (6.7)	2 (4.5)	7 (4.7)
Vulvovaginal Disorder	2 (3.3)	3 (6.7)	1 (2.3)	6 (4.0)

N = total number of subjects in a treatment group; n = number of subjects within a treatment group who had an adverse event.

* A subject may have reported more than 1 adverse event.

Table 12. Blood Pressure (Study Report, pages 106-107)

Treatment Group		Time Period			P value ^a
		Baseline	Visit 9/ Cycle 26 or Final Visit	Change from Baseline	
		Value	Value	Change from Baseline	P value ^a
Systolic Blood Pressure (mm Hg)					
Placebo	N	61	50	50	0.108
	Mean (SD)	122.1 (14.28)	119.0 (13.20)	-2.3 (9.87)	
	Range	92 - 151	94 - 144	-25 - 16	
E ₂ 2.2 mg	N	45	37	37	0.079
	Mean (SD)	122.0 (11.85)	119.0 (13.54)	-3.1 (10.55)	
	Range	99 - 148	90 - 144	-35 - 13	
	P value ^b	0.998		0.901	
E ₂ 4.4 mg	N	44	39	39	0.493
	Mean (SD)	120.4 (12.76)	122.0 (21.75)	2.0 (18.27)	
	Range	94 - 147	92 - 220	-24 - 84	
	P value ^b	0.845		0.220	
Overall	P value ^c	0.851		0.154	
Diastolic Blood Pressure (mm Hg)					
Placebo	N	61	50	50	0.387
	Mean (SD)	77.2 (7.77)	75.6 (7.26)	-1.0 (7.51)	
	Range	60 - 92	60 - 90	-21 - 5	
E ₂ 2.2 mg	N	45	37	37	0.382
	Mean (SD)	78.9 (7.23)	75.4 (8.65)	-1.1 (7.43)	
	Range	65 - 93	56 - 98	-15 - 17	
	P value ^b	0.983		0.972	
E ₂ 4.4 mg	N	44	39	39	0.046 [*]
	Mean (SD)	74.5 (8.36)	78.0 (11.27)	3.2 (9.57)	
	Range	63 - 87	60 - 118	-14 - 38	
	P value ^b	0.182		0.042 [*]	
Overall	P value ^c	0.195		0.030 [*]	

N = number of subjects in treatment group; SD = standard deviation; TMT = treatment.

Number of subjects may vary from visit to visit due to missing data.

^a P Value for change from baseline within treatment group using the paired t-test.

^b P Value for comparison with placebo.

^c Overall treatment P values were obtained from the following model with baseline covariate: Y = TMT CENTER.

^{*} P<0.05.

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Appendix 2.2

Review of Supporting Phase 3 Study (Study Report A10079): "A double-blind, double-dummy, placebo-controlled, randomized study to investigate efficacy and safety of 2 continuously combined transdermal estradiol/levonorgestrel preparations when used for prevention of involutional osteoporosis over 2 years (26 cycles) in postmenopausal women"

Note: This review is based on the original NDA submission and replies to questions in the submission dated 29 July 2005.

Abbreviations (not shown for units of measurement, e.g., mm for millimeter)

AE = adverse event

A-P = anterior-posterior

BMD = bone mineral density

BMI = body mass index

BP = blood pressure

Climara Pro = Climara Pro™ (17-β estradiol/levonorgestrel transdermal system)

DEXA = dual energy x-ray absorptiometry

DM = transdermal system with 17β estradiol 4.5 mg and levonorgestrel 3.75 mg, delivering 17β estradiol 45 mcg and levonorgestrel 40 mcg per day

E = 17β estradiol

EM = transdermal system with 17β estradiol 4.4 and with levonorgestrel 2.75 mg, delivering 17β estradiol 45 mcg and levonorgestrel 30 mcg per day

FSH = follicle stimulating hormone

HARTS = Hoechst Adverse Reactions Terminology System

ITT = intent-to-treat

L = lumbar

LNG = levonorgestrel

Mercury = Hg

RCT = randomized clinical trial

SD = standard deviation

vs. = versus

1. Objectives

The objective of this RCT was to evaluate the efficacy of EM and DM vs. placebo, for the prevention of osteoporosis in postmenopausal women. The primary efficacy variable was the percent change from baseline in BMD of the lumbar spine (A-P view, L2-L4). The secondary efficacy variables included percent changes from baseline in BMD of left hip, non-dominant forearm, and total body; and actual changes from screening in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, urinary urinary calcium). ()
measures C-telopeptide alpha 1 chain of type I collagen.)

Safety was also evaluated, in terms of AEs, laboratory tests, vital signs, physical examinations (including pelvic examinations), cervical cytology smears, endometrial biopsies, and mammography.

2. Patient Population

2.1 Geography and Calendar Time

Patients were recruited at 2 centers in Denmark. The RCT was conducted from 18May99 to 04Jul02.

2.2 Inclusion and Exclusion Criteria

In the discussion below, “previously” or “previous” means before screening or baseline, whichever applies. The information discussed was obtained by history or examination at screening or baseline, and judgments about it were generally made by the investigators.

Inclusion Criteria. Female; ≥ 45 years of age or ≥ 40 with bilateral oophorectomy and ≤ 65 ; 1 to ≤ 3 or > 3 to ≤ 10 years postmenopausal; BMD T-score -1.0 to -2.5 (mean of screening and baseline values) at lumbar spine (A-P view, L2-L4) and/or femoral neck; intact uterus with endometrial thickness ≤ 5 mm by transvaginal ultrasound and endometrial biopsy either negative or inadequate tissue; tolerance of transdermal system during run-in phase of RCT; and signed, informed consent.

Exclusion Criteria. Any condition compromising body systems that could have resulted in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of study drug; severe systemic disease that could have interfered with conduct of the study or interpretation of the results; myocardial infarction in previous 6 months or heart disease severe enough for treatment with drugs for arrhythmia or angina; congestive heart failure; uncontrolled thyroid disorders; current or past history of clinically significant depression; history of stroke or transient ischemic attacks; fasting baseline serum cholesterol > 300 mg/dl or triglycerides > 300 mg/dl; known or suspected malignant or premalignant disease.; history of steroid hormone dependent malignant disease; abnormal, clinically significant findings on gynecological examination which might worsen with hormone treatment (in the opinion of the investigator); cervical smear with Pap \geq III; endometrial thickness > 5 mm by vaginal ultrasound, endometrial biopsy showing hyperplasia or cancer, or history of endometrial hyperplasia or cancer; abnormal baseline laboratory values considered to be clinically significant; history of alcohol or drug abuse in previous 2 years; current, clinically significant liver or kidney disorder; insulin-dependent diabetes mellitus or fasting baseline glucose > 140 mg/dl; hypertension or systolic BP ≥ 160 or diastolic BP ≥ 95 mm hg (sitting); thrombophlebitis, thromboembolic disorder, a history of either, or suspected genetic predisposition; treatment with anticoagulants (heparin or coumadin); endometrial curettage in previous 6 months; sex steroid treatment in previous 4 weeks by oral, transdermal, intrauterine, or intravaginal, or estrogen-implant route, or in previous 6 months by

intramuscular route; participation in another clinical trial in previous 1 month or treatment with an investigational drug in previous 3 months; known or suspected bone disease (including osteoporosis) and/or BMD below - 2.5 or above -1.0 (mean of screening and baseline values), except for a single value; clinical fracture in previous 6 months; immobilization for ≥ 2 or previous 6 months; hypocalcemia, hypercalcemia, and vitamin D deficiencies; systemic treatment with fluoride, calcitonin, pharmacologically active vitamin D derivatives, or bisphosphonates, at any time; chronic systemic treatment with corticosteroids; known allergy or hypersensitivity to transdermal systems or ingredients; and intolerance to study drug during run-in phase of RCT.

2.3 Withdrawal Criteria

Patients had the right to withdraw at any time, without giving reasons. If a patient did withdraw, the reason (if given) was recorded. If study drug had been given, the patient was advised to undergo end-of-study safety evaluations. Patients could be withdrawn for any of the following reasons: SAEs considered to be certainly or possibly related to study drug; BMD loss >6% from baseline to 12 months; first occurrence of migraine headaches or more frequent occurrence of unusually severe headaches; sudden, unexplained onset or worsening of perceptual disorders (e.g., disturbances of vision or hearing); first signs or symptoms of thrombophlebitis or thromboembolic disorders (e.g., unusual swelling of legs, stabbing pain on breathing, coughing for no apparent reason); unexplained onset or worsening of pain and tightness in chest; prolonged immobilization (e.g., after accidents or surgery); onset of jaundice or hepatitis, or generalized pruritis; increase in epileptic seizures; significant rise in BP (in the opinion of the investigator); development of other conditions described as exclusion criteria; allergic reaction to transdermal system; and discretion of the investigator. Reasons for withdrawal were to be documented, any rechallenge was to be discussed in advance with Schering (Sponsor of this RCT), all tests with values that became abnormal and were considered clinically significant were to be repeated until returning to baseline or normally acceptable levels – if a value did not return to an acceptable level, the etiology was to be identified and Schering notified. Withdrawals were not replaced. In addition, the entire RCT could have been cancelled by the trial manager for medical reasons or by Schering if it could not be completed according to the protocol.

2.4 Screening

A total of 296 patients were screened, of whom 214 (72.3%) were randomized. Of the 82 (27.7%) not randomized, the main reasons were the inclusion/exclusion criteria referring to gynecological/breast examinations (n=26), baseline cholesterol/triglyceride levels (n=20, and BMD (n=8), and withdrawal of consent (n=11). See Table 1.

2.5 Randomization and Follow-up

Patients were randomized within strata of years since menopause (1 to ≤ 3 , >3 to ≤ 10) by equal allocation: 71 to EM, 72, to DM, and 71 to placebo. The modified ITT population included the 212 patients randomized who received at least 1 dose of study drug: 69 in

the EM group, 72 in the DM group, and 71 in the placebo group. Of these 212 patients, study drug was discontinued prematurely for 38 (55.1%) in the EM group, 40 (55.6%) in the DM group, and 28 (29.4%) in the placebo group. The higher rates in the EM group and the DM group vs. the placebo group were mainly due to higher rates of AEs.

2.6 Patients Analyzed

Efficacy and safety were analyzed for a “full analysis set (FAS),” consisting of all patients in the modified ITT population. Efficacy was also analyzed for a per protocol set.

Efficacy was analyzed and presented according to the randomization strata by years since menopause (1 to ≤ 3 , >3 to ≤ 10). Other stratifications were also done.

3. Calcium and Vitamin D

All patients received 500 mg of calcium daily. Vitamin D supplements were not provided and vitamin D levels were not measured.

4. RCT Conduct, Data Collection, and Data Analysis

The methods used to conduct the RCT, for the collection of data, and for the analysis were typical for Phase 3 RCTs.

For the schedule of events, see Table 2.

5. Results

The results discussed below are for screening or baseline, whichever applies, and for the FAS at week 104 or “Last Visit,” which means the last observation on study drug carried forward. Other analyses were also done.

5.1 Baseline Characteristics

Patients in the EM Group, DM group, and placebo group were similar at baseline by age, BMI, height, weight, ethnic group, BMD of the femoral neck and lumbar spine (A-P view, L2-L4), and other baseline characteristics. Of the 212 patients in the FAS, only 7 (3.3%) had undergone bilateral oophorectomy. E2 was not measured. See Table 3.

5.2 Efficacy

The Results for BMD refer to measurement by DEXA. Results are discussed for the FAS, to the nearest decimal point except where otherwise specified. See statistical review by Dr. Mele for further information.

5.2.1 Main Efficacy Results from Berlex Analyses

For the numbers of FAS patients in the EM group, DM group, and placebo group by years since menopause (1 to ≤ 3 , >3 to ≤ 10) at baseline, see Table 4.

Lumbar Spine. In women at 1 to ≤ 3 years since menopause, baseline mean BMD in mg HA/cm³ was 1.0 in the EM group, DM group, and placebo group. At Last Visit, the mean percent change from baseline was 3.8% in the EM group, 4.2% in the DM group, and -2.6% in the placebo group ($p < 0.05$ for both EM and DM vs. placebo). In women ≥ 3 to ≤ 10 years since menopause, baseline mean BMD in mg HA/cm³ was 1.0 in the EM group, DM group, and placebo group. At Last Visit, the mean percent change from baseline was 4.6% in the EM group, 5.2% in the DM group, and -1.6% in the placebo group ($p < 0.05$ for both EM and DM vs. placebo). See Table 5.

Left Hip, Non-dominant Forearm, and Total Body. In the left hip and total body, BMD increased in the EM group and the DM group vs. the placebo group. However, in the non-dominant radius, the results were inconsistent. See Table 6.

Reviewer Comment on 5.2.1 Main Efficacy Results from Berlex Analyses

The Last Visit results for the lumbar spine were based on 200 the 212 patients in the FAS. I asked Berlex to clarify accounting for the other patients in the FAS. Berlex replied that 12 patients had no postbaseline lumbar spine BMD measurements. (Submission dated 29 July 2005, page 5)

5.2.2 Efficacy Results from Analyses Requested by Division

in the pre-NDA meeting, the Division said that "the pivotal and supportive trial reports should include evaluation of efficacy according to endogenous (baseline) estradiol. The cut-off with data in the literature is 5 pg/ml. Other cut-offs may also be considered." See attached Minutes of 13Oct04 Pre-NDA Meeting.

For the supportive trial, Berlex could not provide such evaluation because E2 was not measured.

5.2.3 Other Efficacy Results

Other analyses of BMD and analyses of biochemical markers of bone metabolism were supporting of the efficacy results described above. (Study Report, pages 98-129)

5.3 Safety

All safety analyses refer to the FAS. See Table 2 for schedule of evaluations.

5.3.1 Extent of Exposure

Enough transdermal systems (patches) were to be dispensed for 104 weeks or 728 days of treatment per patient, according to the protocol. Patients could receive more if needed due to adhesion or cosmetic problems.

Table 8 shows the mean (SD) number of transdermal systems (patches) applied and mean number of days with patch wear for the EM group, DM group, and placebo group. The mean number of days with patch wear/728 were 456.7/728 (62.7%) for the EM group, 729.9/728 (100.3%) for the DM group, and 527.5/728 (72.5%) for the placebo group.

Reviewer Comment on 5.3.1 Extent of Exposure

I asked Berlex for more information about the difference in mean number of days with patch wear for the DM group vs. the EM group and the placebo group. Berlex replied that the mean number of days with patch wear for the DM group was 429.9 instead of 729.9 as cited above from the original NDA submission. (Submission dated 29 July 2005, page 5) So, the mean number of patch days/728 for the DM group was 429.9/728 ((59.1%).

3.2 Adverse Events (AEs)

The discussion below refers to AEs that occurred <225 days after stopping study drug, except where otherwise specified.

5.3.2.1 Deaths

There was a total of 1 death, in the EM group: a 52-year old year old woman with a history of alcohol abuse was found dead. An autopsy revealed intake of methadone and diazepam.

5.3.2.2 Serious Adverse Events (SAEs)

There were 5 (7.2%) patients in the EM group, 3 (4.2%) patients in the DM group, and 5 (7.0%) patients in the placebo group with SAEs (including the death). Of the 5 patients in the EM group, 1 had carcinoma of the rhinopharynx, 1 had malignant melanoma, 1 had an ovarian cyst, 1 had depression, and 1 was found dead (see above). Of the 3 patients in the DM group, 2 had ovarian cysts and 1 had syncope and vaginal hemorrhage. Of the 5 patients in the placebo group, 1 had an abscess of the appendix, 1 had pneumonia, 1 had cholelithiasis, 1 had neuralgia, and 1 had deep thrombophlebitis in a leg. See Table 8.

5.3.2.3 Discontinuation Due to AEs

There were 31 (44.9%) patients in the EM group, 37 (51.4%) patients in the DM group, and 18 (25.4%) patients in the placebo group who discontinued study drug due to AEs. This included 15 (21.7%) patients in the EM group, 22 (30.6%) patients in the DM group, and no patients in the placebo group who discontinued due to vaginal hemorrhage. There were 2 (2.9%) patients in the EM group, no patients in the DM group, and no patients in the placebo group who discontinued due to endometrial disorder. There were no other meaningful differences between the 3 groups. Most of the other discontinuation were due to application site reactions: 8 (11.6%) in the EM group, 12 (16.6%) in the DM group, and 14 (19.7%) in the placebo group. See Table 9.

5.3.2.4 Any AE

There were 69 (100%) patients in the EM group, 70 (97.2%) patients in the DM group, and 69 (97.2%) patients in the placebo group with any AE.

For AEs in $\geq 5\%$ of patients in any of the 3 groups, there were meaningful differences between the 3 groups for osteoporosis, hot flashes, sinusitis, breast pain, eczema, endometrial disorder, and vaginal hemorrhage. See Table 10.

Osteoporosis. There were no patients in the EM group, no patients in the DM group, and 5 (7.0%) patients in the placebo group with osteoporosis.

Hot Flashes. There were 1 (1.4%) patient in the EM group, 1 (1.4%) patient in the DM group, and 6 (8.5%) patients in the placebo group with hot flashes.

Sinusitis. There were 2 (2.9%) patients in the EM group, 1 (1.4%) patient in the DM group, and 7 (9.9%) patients in the placebo group with sinusitis.

Breast Pain. There were 12 (17.4%) patients in the EM group, 22 (30.6%) patients in the DM group, and 2 (2.8%) patients in the placebo group with hot flashes.

Eczema. There were 2 (2.9%) patients in the EM group, 4 (5.6%) patients in the DM group, and no patients in the placebo group with eczema.

Endometrial Disorder. There were 6 (8.7%) patients in the EM group, 4 (5.6%) patients in the DM group, and 1 (1.4%) patients in the placebo group with endometrial disorder.

Vaginal Hemorrhage. There were 16 (23.2%) patients in the EM group, 24 (33.3%) patients in the DM group, and no patients in the placebo group with vaginal hemorrhage.

Application Site Reaction. There were 34 (49.3%) patients in the EM group, 29 (40.3%) patients in the DM group, and 48 (67.6%) patients in the placebo group with application site reactions.

Reviewer Comment on 5.3.2 Adverse Events (AEs)

There were no meaningful differences in deaths or SAEs between the EM group, DM group, and placebo group. Expected effects of estrogen and/or progestin appear to account for the higher rates of discontinuation for vaginal hemorrhage and Any AE called breast pain or endometrial disorder, and the lower rates of Any AE called osteoporosis or hot flashes, in the EM group and the DM group vs. the placebo group.

Reasons for the lower rate of Any AE called sinusitis in the EM group and the DM group vs. the placebo group are not clear.

For application site reactions, the substantial rates discontinuation and high rates of Any AE in the EM group, DM group, and placebo group suggest that acceptability of the transdermal system may be somewhat limited in postmenopausal women.

5.3.3 Clinical Laboratory Tests

The hematology, blood chemistry, and urinalysis variables are listed below. These were reviewed in tables of frequencies of patients with values below normal, within normal limits, and above normal, and tables of mean, median, minimum, and maximum values. There were no differences between the 3 groups that raised safety concerns. Values below normal for alkaline phosphatase, inorganic phosphate, and triglycerides were more frequent in the EM group and the DM group vs. the placebo group, and values above normal for low-density lipoprotein cholesterol and total cholesterol were less frequent in the EM group and the DM group vs. the placebo group. (Study Report, pages 145-153)

Hematology – red cell count, hematocrit, hemoglobin, platelet count, white cell and differential count.

Blood Chemistry – sodium potassium chloride, glucose, urea nitrogen, creatinine, calcium phosphorus, total bilirubin, total protein, albumin, liver function tests: gamma-glutamyltransferase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and lipids: triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol.

Urinalysis – leukocytes, erythrocytes, pH, glucose, and protein.

5.3.4 Weight and Vital Signs

The variables were weight, heart rate, systolic BP, and diastolic BP. These were reviewed for the EM group, DM group, and placebo group in tables of mean, median, minimum, and maximum values, and mean, median, minimum, and maximum changes from baseline. There were no meaningful differences between the 3 groups. (Study Report, pages 1393-1400)

5.3.5 Physical Examinations (including Pelvic)

Examinations were done for general appearance, skin, eyes/ears/nose/throat, head and neck, lungs, heart, abdomen, lymph nodes, musculoskeletal, neurological, external genitalia, pelvic, and breasts. These were reviewed in tables of frequencies of normal, abnormal, and not done/unknown/not available. There were no meaningful differences between the 3 groups. See Table 11 for results of pelvic, external genitalia, and breast examinations. (Study Report, pages 157-158)

5.6.6 Mammography

Results were reviewed in tables of frequencies of normal, abnormal, and not done/unknown/not available. There were no meaningful differences between the 3 groups. See Table 12. (Study Report, page 158)

5.3.7 Cervical Cytology

Results were reviewed in tables of frequencies of CI or II, C III, and not done/unknown/not available. There were no patients with C III results at screening, and there were 1 (1.4%) patient in the EM group, 2 (2.8%) patients in the DM group, and no patients in the placebo group with C III results at Last Visit. Of these 3 patients, 2 had epithelial dysplasia and 1 had atypical cells. See Table 13. Of the 2 patients in the DM group with C III results, 1 received a diagnosis of cervical dysplasia, underwent colposcopy and cryotherapy, and was considered to need no further follow-up. (Study Report, page 159)

5.6.8 Vaginal Bleeding

The mean number of days with bleeding/spotting in the first 90 days was 15 (SD=16) in the EM group and 19 (SD=18) in the DM group, and in the last 90 days was decreased to 7 in both groups. The number of bleeding/spotting episodes in the first 90 days was 3 in both the EM group and the DM group, and in the last 90 days was decreased to 2 in the EM group and 1 in the DM group. The maximum length of bleeding/spotting episodes in the first 90 days was 11 in the EM group and 14 in the DM group, and in the last 90 days was about 50% lower in both groups. Bleeding/spotting was negligible in the placebo group. The results above are to the nearest day. (Study Report, pages 154-155)

Reviewer Comment on 5.6.8 Vaginal Bleeding

Expected effects of estrogen with progestin appear to account for the higher rates of vaginal bleeding in the EM group and the DM group vs. the placebo group.

5.6.9 Endometrial Biopsy and Transvaginal Ultrasound

The endometrial biopsies were read centrally by 2 pathologists and if no consensus was reached, a 3rd pathologist was consulted. In patients whose Last Visit biopsy results were

"insufficient tissue for diagnosis," the results of transvaginal ultrasound were considered, and if the endometrial thickness was <5 mm, the diagnosis was "inactive/atrophic endometrium."

Biopsies were obtained at screening, for 62 (89.9%) patients in the EM group, 64 (88.9%) patients in the DM group, and 57 (80.3%) patients in the placebo group, and at Last Visit for 34 (49.3%) patients in the EM group, 45 (62.5%) patients in the DM group, and 47 (66.2%) patients in the placebo group. The main reason given for women not having biopsies at screening or Last Visit was stenosis uteri.

In the main central readings of endometrial biopsies and transvaginal ultrasound at Last Visit, there were no diagnoses of hyperplasia or cancer, and there were 3 (4.4%) patients in the EM group, 2 (4.4%) patients in the DM group, and no patients in the placebo group with proliferative endometrium. In later central readings, polyps were reported for 1 patient in the EM group with proliferative endometrium and 1 patient in the DM group with atrophic endometrium, and squamous or papillary mucinous metaplasia was reported for 1 patient in the DM group with atrophic endometrium. See Table 14.

Reviewer Comment on 5.6.9 Endometrial Biopsy and Transvaginal Ultrasound

Expected effects of estrogen (even with progestin) appear to account for the higher rates of endometrial proliferation in the EM group and the DM group vs. the placebo group.

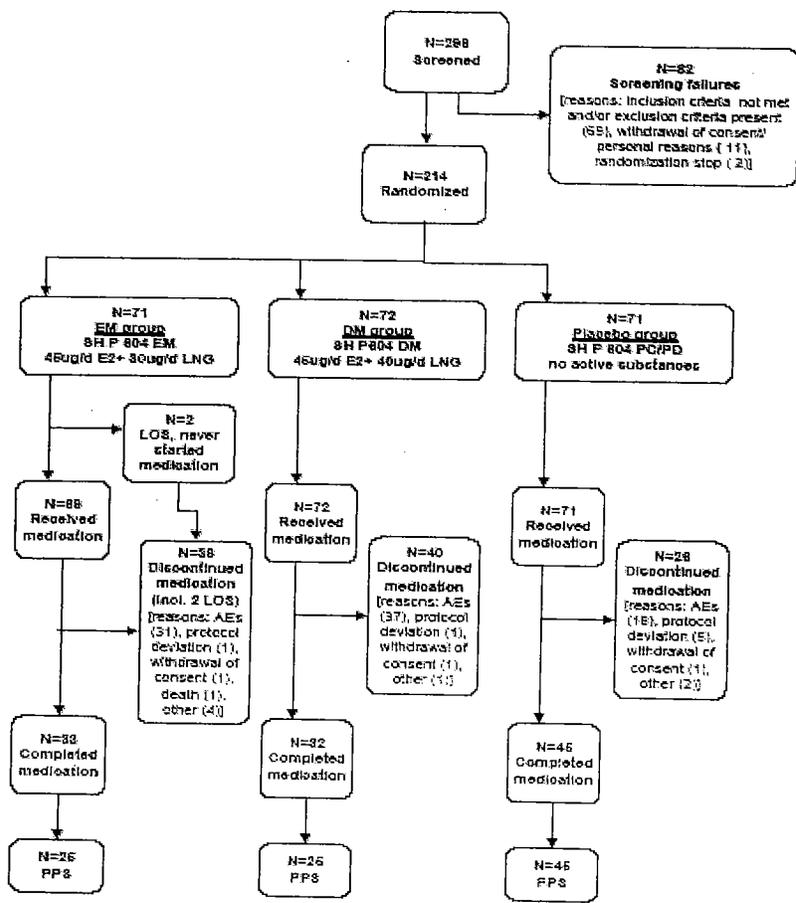
I asked Berlex for more information about the low rate of biopsies at Last Visit because I could not find good support for stenosis uteri as the main reason, in Study Table 249, which was cited. Berlex replied that Table 259 lists all patients without biopsies and supports stenosis uteri as the main reason.

6. Discussion

Efficacy. The efficacy results of the RCT support those of the pivotal trial, with similar limitations.

Safety. There were no unexpected results and the RCT raised no safety concerns.

Table 1. Patient Disposition (Study Report, pages 84-85)



Reason for screening failure	Number of patients
Inclusion criteria not met (see section 9.3.1) and/or exclusion criteria present (see section 9.3.2)	69
Inclusion criterion no. 4 / exclusion criteria nos.11-13 (intact uterus and endometrium ≤5mm, normal PAP and biopsy, normal gynecological/breast examination)	26
Exclusion criterion no. 8 (baseline cholesterol/triglyceride levels)	20
Inclusion criterion no. 3 / exclusion criterion no. 14 (BMD within osteopenic range)	8
Exclusion criterion no. 18 (baseline blood pressure)	4
Exclusion criterion no. 9 (Malignant or premalignant disease)	2
Exclusion criterion no. 19 (thrombophlebitis or thromboembolic disorders)	2
Exclusion criterion no. 15 (clinical fracture)	2
Exclusion criterion no. 1 (Skin diseases or conditions comprising the function of absorption)	1
Inclusion criterion no. 2 (more than 10 years after menopause)	1
Inclusion criterion no. 5 / exclusion criterion no. 31 (tolerance to placebo patch)	1
Exclusion criterion no. 6 (depression)	1
Exclusion criterion no. 14 (baseline laboratory values)	1
Withdrawal of consent	11
Randomization stop (in this stratum)	2
Total	82

Table 2. RCT Schedule of Events (Study Report, page 54)

Trial Evaluations	Week time frame: Day -8 up to -84 days	0	4	12	24	52	76	104
			+4d	+7d	+12d	+12d	+12d	+12d
	cycle of 28 days:-1	0	1	3	6	13	19	26
	Visits : 1	2	3	4	5	6	7	8*
	Screen	Baseline	Treatment Period					
Patient information	x							
Informed Consent	x							
Medical / medication history	x							
Gynecological history	x							
Demographic data	x							
Check of in-/exclusion criteria	x	x						
Randomization		x						
Heart rate, blood pressure, weight	x	x	x	x	x	x	x	x
Physical exam / height	x					x		x
Physical activity, nutrition (esp. calcium)		x				x		x
Smoking / alcohol	x					x		x
Gynecological exam.	x				x	x	x	x
Mammography**	x							x
Cervical smear***	x							x
Transvaginal ultrasound	x				x	x	x	x
Endometrial biopsy (may be repeated at any time at the discretion of the investigator)	x							x
General laboratory	x				x	x		x
Parameters of bone metabolism	x	x	x	x	x	x		x
Bone densitometry	x	x		x	x	x	x	x
Calcaneus ultrasound*		x		x	x	x	x	x
X-ray spine****	x							
Adverse events including fractures		x	x	x	x	x	x	x
Concomitant medication		x	x	x	x	x	x	x
End of study evaluation								x
Diary cards dispensed		x						
Diary cards returned/reviewed			x	x	x	x	x	x
Placebo patch dispensed	x							
Tolerance to placebo patch		x						
Medication (incl. calcium suppl.) dispensed		x	x	x	x	x	x	
Medication returned			x	x	x	x	x	x

*If the patient is prematurely withdrawn from the trial, all evaluations described under Visit 8 must be performed at the final visit.

**Mammography may have been performed within the last year prior to Visit 1 (provided the report is available).

***Cervical smear may have been performed within the last three months prior to Visit 1 (provided the report is available).

****The x-ray of the spine will be repeated at any visit when a vertebral fracture is suspected and may have been performed within the last 12 weeks prior to Visit 1 (provided the report is available)

* measurement has been eliminated in one center and at Visit 1 in both centers (see amendment no. 1, section 9.3.1)

Climara Pro®/17-β estradiol an levonorgestrel, USP

Table 3. Baseline Characteristics (Study Report, pages 90, 253, 323)

	EM (n=69)		DM (n=72)		Placebo (n=71)		Overall (n=212)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	54.1	3.0	55.1	3.2	54.6	2.7	54.6	3.0
BMI (kg/m ²)	24.24	3.35	24.62	3.48	25.04	3.54	24.64	3.46
Height (cm)	164.93	5.22	165.01	6.59	164.86	6.72	164.93	6.20
Weight (kg)	65.93	9.32	67.06	10.35	67.97	9.53	67.00	9.74

	SH P 604 EM / SH P 604 PC		SH P 604 DM / SH P 604 PD		SH P 604 PC / SH P 604 PD		Overall
Number of patients	69 (100.0%)		72 (100.0%)		71 (100.0%)		212 (100.0%)
Ethnic Group							
caucasian	68 (100.0%)		71 (96.6%)		71 (100.0%)		210 (99.5%)
black	0 (0.0%)		1 (1.4%)		0 (0.0%)		1 (0.5%)

	SH P 604 EM / SH P 604 PC		SH P 604 DM / SH P 604 PD		SH P 604 PC / SH P 604 PD		Overall
Number of patients	69 (100.0%)		72 (100.0%)		71 (100.0%)		212 (100.0%)
no yes, unilateral	68 (96.6%) 1 (1.4%)		70 (97.2%) 2 (2.8%)		67 (94.4%) 4 (5.6%)		205 (96.7%) 7 (3.3%)

	SH P 604 EM / SH P 604 PC		SH P 604 DM / SH P 604 PD		SH P 604 PC / SH P 604 PD		Overall
Number of patients	69 (100.0%)		72 (100.0%)		71 (100.0%)		212 (100.0%)
1-<3 years	33 (47.8%)		31 (43.1%)		31 (43.7%)		95 (44.6%)
3-<10 years	36 (52.2%)		41 (56.9%)		40 (56.3%)		117 (55.2%)

Pre-treatment BMD T-scores for the femoral neck and for the lumbar spine region L2-L4 (FAS)

	EM (n=69)		DM (n=72)		Placebo (n=71)		Overall (n=212)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Femoral neck	-0.714	0.785	-0.494	0.757	-0.604	0.760	-0.603	0.769
Lumbar spine (L2-L4)	-1.227	0.686	-1.214	0.611	-1.184	0.677	-1.208	0.655

Pre-treatment BMD T-scores for the femoral neck and for the lumbar spine region L2-L4 (PPS)

	EM (n=25)		DM (n=25)		Placebo (n=36)		Overall (n=86)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Femoral neck	-0.798	0.714	-0.538	0.676	-0.705	0.726	-0.684	0.707
Lumbar spine (L2-L4)	-1.373	0.671	-1.428	0.510	-1.326	0.532	-1.374	0.565

Table 4. Number of Patients in Efficacy Analyses by Years Since Menopause
(Study Report, page 89)

Analysis Set	Partition 1 *)	EM	DM	Placebo	Overall
FA5	All patients	69	72	71	212
	Subgroup 1A	33	31	31	95
	Subgroup 1B	36	41	40	117

*) Subgroup 1A: Patients more than one and up to three years after menopause
Subgroup 1B: Patients more than three and up to ten years after menopause

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Table 5. Percent Change from Baseline, Lumbar Spine BMD (A-P View, L2-L4), by Years Since Menopause (Study Report, page 99)

FAS / Partition 1		SHP 604 EM	SHP 604 DM	Placebo
Subgroup 1A¹⁾				
Baseline [mg/HA cm ²]	N	33	31	31
	Mean (SD)	1.031 (0.084)	1.040 (0.076)	1.044 (0.078)
% change at Week 104	N	15	11	19
	Mean (SD)	5.351 (4.089)	6.141 (2.278)	-3.462 (3.129)
% change at individual last visit	N	33	28	29
	Mean (SD)	3.819 (3.965)	4.193 (2.719)	-2.605 (3.551)
Subgroup 1B²⁾				
Baseline [mg/HA cm ²]	N	36	41	40
	Mean (SD)	1.027 (0.092)	1.025 (0.080)	1.026 (0.101)
% change at Week 104	N	18	22	27
	Mean (SD)	5.760 (4.233)	7.210 (3.301)	-1.363 (2.887)
% change at individual last visit	N	35	37	38
	Mean (SD)	4.640 (3.720)	5.228 (4.155)	-1.588 (2.876)

1) Subgroup 1A: Patients more than one and up to three years after menopause

2) Subgroup 1B: Patients more than three and up to ten years after menopause

Results from one-sided Dunnett's test:
 Difference between means compared to placebo
 and lower limit of simultaneous one-sided 95% confidence interval (CI)

FAS / Partition 1	Difference between means [lower limit of simultaneous one-sided 95% CI]	
	SHP 604 EM versus placebo	SHP 604 DM versus placebo
Subgroup 1A¹⁾		
% change at week 104	9.313 [5.985] (*)	9.603 [7.049] (*)
% change at individual last visit	6.424 [4.704] (*)	6.798 [5.007] (*)
Subgroup 1B²⁾		
% change at week 104	7.123 [5.158] (*)	8.572 [6.717] (*)
% change at individual last visit	6.228 [4.669] (*)	6.816 [5.273] (*)

1) Subgroup 1A: Patients more than one and up to three years after menopause

2) Subgroup 1B: Patients more than three and up to ten years after menopause

(*) Significant difference to placebo at 5% level (One-sided Dunnett test performed within the framework of a two-factorial analysis of variance model considering treatment, center and treatment by center interaction)

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Table 6. Absolute and Percent Changes from Baseline, Left Hip, Non-dominant Forearm, and Total Body, by Years Since Menopause (Study Report; page113)

FAS / Partition 1	SH P 604 EM		SH P 604 DM		Placebo	
	1 to ≤3 yrs postmenopause	>3 to ≤10 yrs postmenopause	1 to ≤3 yrs postmenopause	>3 to ≤10 yrs postmenopause	1 to ≤3 yrs postmenopause	>3 to ≤10 yrs postmenopause
BMD of left hip						
Week 12	0.004 (0.5)	0.012 (1.3)	0.006 (0.6)	0.011 (1.2)	-0.001 (-0.1)	0.004 (0.4)
Week 52	0.017 (2.0)	0.025 (2.9)	0.020 (2.2)	0.023 (2.5)	-0.008 (-0.8)	-0.001 (-0.2)
Week 104	0.034 (4.1)	0.039 (4.4)	0.029 (3.3)	0.040 (4.5)	-0.023 (-2.6)	-0.006 (-0.7)
Individual last visit	0.016 (1.9)	0.030 (3.4)	0.019 (2.1)	0.027 (3.1)	-0.017 (-1.8)	-0.004 (-0.5)
BMD of non-dominant forearm						
Week 12	0.002 (0.6)	0.005 (1.3)	0.005 (1.1)	-0.001 (-0.1)	0.005 (1.1)	0.004 (1.1)
Week 52	0.005 (1.3)	0.014 (3.5)	0.004 (1.2)	0.012 (3.1)	0.005 (1.2)	0.007 (1.7)
Week 104	0.006 (1.5)	0.015 (3.4)	0.009 (2.4)	0.009 (2.3)	-0.009 (-1.8)	0.009 (2.1)
Individual last visit	0.004 (1.1)	0.009 (2.2)	0.008 (1.8)	0.008 (2.0)	-0.004 (-0.8)	0.008 (2.0)
BMD of total body						
Week 12	0.002 (0.2)	0.003 (1.3)	0.003 (0.3)	0.009 (1.2)	-0.002 (-0.1)	-0.001 (0.4)
Week 52	0.011 (1.1)	0.005 (0.5)	0.004 (0.4)	0.006 (0.5)	-0.019 (-1.7)	-0.006 (-0.6)
Week 104	0.011 (1.1)	0.009 (0.8)	0.005 (0.5)	0.006 (0.7)	-0.035 (-3.2)	-0.015 (-1.4)
Individual last visit	0.008 (0.8)	0.010 (1.0)	0.007 (0.6)	0.005 (0.6)	-0.026 (-2.4)	-0.011 (-1.1)

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Table 7. Extent of Exposure to Study Drug (Study Report, page 98)

Mean number of patches applied and mean number of days with patch wear

	Analysis set	n	Number of patches applied		Number of days with patch wear	
			Mean	SD	Mean	SD
EM group	FAS	69	144.8	86.8	456.7	272.4
DM group	FAS	70	137.4	96.9	729.9	295.7
Placebo group	FAS	71	170.1	82.5	527.5	256.1

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Table 8. Serious Adverse Events (SAEs) (Study Report, page 142)

Listing of SAEs by patient and treatment (FAS)

Treatment	Subj. no.	HARTS term(s) of SAE	Visit on which SAE was reported	Drug relationship (Investigator's assessment)	Intensity	Details on SAE
EM	18	CARCINOMA	Week 10‡	Unlikely	Severe	Tumor in rhinopharynx, curative chemotherapy
	235	SKIN MELANOMA	Week 10‡	None	Severe	Malignant melanoma, surgery
	261	OVARIAN CYST	Week 5‡	None	Moderate	Cyst and left ovary removed, surgery
	271	DEPRESSION	Week 10‡	None	Severe	Hospitalization
	332	DEATH	Week 10‡	ND/NA/UNK*	Severe	Unknown cause of death *
DM	229	OVARIAN CYST	Week 7‡	Possible	Moderate	Ovarian cyst left site 8.2*5.3 cm, benign, surgery
	230#	SURGERY	Week 1‡	None	Mild	Hole in membrana tympani, surgery
	298	UROGENITAL NEOPLASM	Week 5‡	Possible	Moderate §	Ovarian cyst left site 8.6*4.2 cm, surgery
	315	SYNCOPE VAGINAL HEMORRHAGE	Week 10‡	Unlikely Probable	Severe Severe	Black-out, hospitalization abrasio uretri (surgery)
	Placebo	3	ABSCESS	Week 10‡	Unlikely	Moderate
Placebo	47	PNEUMONIA	Week 24	None	Severe	Antibiotics, medication
	110	CHOLELITHIASIS	Week 24	None	Moderate	Gallstones lead to cholecystectomy (surgery), medication
	233	NEURALGIA	Week 7‡	None	Moderate	Increased ischiatic pain, right side, hospitalization, medication
	324	DEEP THROMBOPHLEBITIS OF THE LEG	Week 10‡	Probable	Severe	Medication

* not done/ not available/unknown: Unknown cause of death: this patient died after chronic alcohol abuse and methadone misuse / abuse with unclear intention of suicide

No case: this 'SAE' was erroneously entered into the database; as the hole of the membrana tympani was a pre-existing condition and surgery was planned before study start.

§ The SAE of subject no. 298 was assessed as mild by the investigator in Oct 2000, but as moderate on the respective AE form (of May 2000). Due to the many changes in responsibility on the site and changing investigators assessing the patient it was decided by study manager and CRA to enter the worse assessment into the database.

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Table 9. Discontinuations Due To AEs (Study Report, page 1095-1096)

Events (HARTS)	SM P 604 EM	SM P 604 EM	SM P 604 PC	Overall
	/ SM P 604 PC	/ SM P 604 FO	/ SM P 604 PD	
ANY EVENT	31/69 (44.9%)	37/72 (51.4%)	10/71 (25.4%)	66/212 (40.6%)
BODY/ABDO				
ANY EVENT	0/69 (0.0%)	1/72 (1.4%)	0/71 (0.0%)	1/212 (0.5%)
Abdominal pain	0/69 (0.0%)	1/72 (1.4%)	0/71 (0.0%)	1/212 (0.5%)
BODY/GEN				
ANY EVENT	1/69 (1.4%)	1/72 (1.4%)	0/71 (0.0%)	2/212 (0.9%)
Sarcinoma	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
Pain	0/69 (0.0%)	1/72 (1.4%)	0/71 (0.0%)	1/212 (0.5%)
CV/VASC/HP				
ANY EVENT	0/69 (0.0%)	0/72 (0.0%)	1/71 (1.4%)	1/212 (0.5%)
Hypertension	0/69 (0.0%)	0/72 (0.0%)	1/71 (1.4%)	1/212 (0.5%)
CV/VASC/GEN				
ANY EVENT	0/69 (0.0%)	0/72 (0.0%)	1/71 (1.4%)	1/212 (0.5%)
Deep thrombophlebitis of the leg	0/69 (0.0%)	0/72 (0.0%)	1/71 (1.4%)	1/212 (0.5%)
DIS/LIV				
ANY EVENT	0/69 (0.0%)	0/72 (0.0%)	1/71 (1.4%)	1/212 (0.5%)
Liver function test abnormal	0/69 (0.0%)	0/72 (0.0%)	1/71 (1.4%)	1/212 (0.5%)
HAEM/HE				
ANY EVENT	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
Peripheral edema	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
MS/MS				
ANY EVENT	0/69 (0.0%)	1/72 (1.4%)	0/71 (0.0%)	1/212 (0.5%)
Myalgia	0/69 (0.0%)	1/72 (1.4%)	0/71 (0.0%)	1/212 (0.5%)
NER/ANS/BSM/L				
ANY EVENT	1/69 (1.4%)	0/72 (0.0%)	1/71 (1.4%)	2/212 (0.9%)
Hot flashes	1/69 (1.4%)	0/72 (0.0%)	1/71 (1.4%)	2/212 (0.9%)
NER/ONS/O				
ANY EVENT	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
Emotional lability	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
RES/GEN				
ANY EVENT	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
Upper respiratory infection	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
SKIN/DERM/MYP				
ANY EVENT	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
Skin melanoma	1/69 (1.4%)	0/72 (0.0%)	0/71 (0.0%)	1/212 (0.5%)
SKIN/GEN				
ANY EVENT	0/69 (0.0%)	12/72 (16.7%)	14/71 (19.7%)	24/212 (16.0%)
Application site reaction	0/69 (0.0%)	12/72 (16.7%)	14/71 (19.7%)	24/212 (16.0%)
UG/FG/UTRS				
ANY EVENT	2/69 (2.9%)	0/72 (0.0%)	0/71 (0.0%)	2/212 (0.9%)
Endometrial disorder	2/69 (2.9%)	0/72 (0.0%)	0/71 (0.0%)	2/212 (0.9%)
UG/FG/VAG				
ANY EVENT	15/69 (21.7%)	22/72 (30.6%)	0/71 (0.0%)	37/212 (17.5%)
Vaginal hemorrhage	15/69 (21.7%)	22/72 (30.6%)	0/71 (0.0%)	37/212 (17.5%)

Note: events are given as HARTS Body-System 1 / HARTS Text English

Table 10. Any AE Reported for ≥5% of Patients in Any Group
(Study Report, pages 1085-1086)

Events (HARTS)	SH		SH		SH	
	P	604 EM / FC	P	604 DM / FD	P	604 PC / FO
BODY/ABDO						
Abdominal pain	4/59	(5.0%)	11/72	(15.3%)	7/71	(9.9%)
BODY/BACK						
Back pain	6/59	(6.7%)	4/72	(5.6%)	5/71	(7.0%)
BODY/GEN						
Flu syndrome	12/59	(17.4%)	9/72	(12.5%)	10/71	(14.1%)
Infection	1/59	(1.4%)	1/72	(1.4%)	5/71	(7.0%)
Pain	1/59	(1.4%)	4/72	(5.6%)	0/71	(0.0%)
Surgery	0/59	(0.0%)	6/72	(8.3%)	1/71	(1.4%)
DIG/EC						
Constipation	2/59	(2.9%)	3/72	(4.2%)	4/71	(5.6%)
Diarrhea	0/59	(0.0%)	4/72	(5.6%)	4/71	(5.6%)
DIS/GEN						
Nausea	1/59	(1.4%)	5/72	(6.9%)	3/71	(4.2%)
MAN/LIP						
MAN/WT						
MS/BON/GEN						
Osteoporosis	0/59	(0.0%)	0/72	(0.0%)	5/71	(7.0%)
MS/JNT						
Arthralgia	1/59	(1.4%)	4/72	(5.6%)	4/71	(5.6%)
NER/ANS/SYM/L						
Hot flashes	1/59	(1.4%)	1/72	(1.4%)	6/71	(8.5%)
NER/CNS/D						
NER/GEN						
Headache	3/59	(4.8%)	6/72	(8.3%)	5/71	(7.0%)
RES/GEN						
Upper respiratory infection	17/59	(24.6%)	16/72	(25.0%)	20/71	(29.0%)
RES/LUNG						
Pneumonia	4/59	(5.0%)	4/72	(5.6%)	6/71	(11.8%)
RES/NASE						
Pharyngitis	5/59	(7.0%)	2/72	(2.0%)	2/71	(2.0%)
RES/SINS						
Sinusitis	2/59	(2.9%)	1/72	(1.4%)	7/71	(9.9%)
SKIN/DRST						
Breast pain	12/59	(17.4%)	22/72	(30.6%)	2/71	(2.0%)
SKIN/DERM/GEN						
Itchiness	2/59	(2.9%)	4/72	(5.6%)	0/71	(0.0%)
SKIN/DERM/VS						
Herpes simplex	4/59	(5.0%)	0/72	(0.0%)	2/71	(2.0%)
SKIN/GEN						
Application site reaction	34/59	(49.8%)	25/72	(40.8%)	40/71	(57.6%)
UG/FG/MENS						
Dysmenorrhea	5/59	(7.2%)	5/72	(5.9%)	0/71	(0.0%)
UG/FG/USGX						
UG/FG/USAS						
Endometrial disorder	6/59	(6.7%)	4/72	(5.6%)	1/71	(1.4%)
Uterine fibroids enlarged	3/59	(4.8%)	6/72	(8.3%)	3/71	(4.2%)
UG/FG/VAS						
Leukorrhea	5/59	(7.2%)	6/72	(8.3%)	4/71	(5.6%)
Vaginal hemorrhage	16/59	(23.2%)	24/72	(39.8%)	0/71	(0.0%)
UG/UT/D/M						
Cystitis	6/59	(5.7%)	6/72	(8.2%)	4/71	(5.6%)

Note: events are given as HARTS Body-System / HARTS Text English

Table 11. Pelvic, External Genitalia, and Breast Examinations
 (Study Report, page 158)

Proportion of patients [%] with abnormal gynecological examination findings by treatment

	EM			DM			Placebo			Overall		
	Screening	Week 24	Week 104									
n	69	54	69	72	46	72	71	60	65	212	160	212
Pelvic	13.0	16.7	10.1	15.3	17.4	13.9	18.3	11.7	14.1	15.6	15.0	12.7
External genitalia	1.4	0	1.4	1.4	0	1.4	1.4	1.7	2.8	1.4	0.6	1.9
Breasts	1.4	1.9	1.4	0	0	0	4.2	3.3	1.4	1.9	1.9	0.9

n = number of patients

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Table 12. Mammography (Study Report, pages 1364-1366)

Mammography by treatment and visit

Timepoint		2M P 604 2M	2M P 604 2M	2M P 604 PC	Overall
		/ 2M P 604 PC	/ 2M P 604 PD	/ 2M P 604 PD	
Screening	Number of patients	69 (100.0%)	72 (100.0%)	71 (100.0%)	212 (100.0%)
	Mammography				
	normal	69 (100.0%)	71 (98.6%)	71 (100.0%)	211 (99.5%)
	abnormal	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.5%)
	ND/UNK/NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Final	Number of patients	69 (100.0%)	72 (100.0%)	71 (100.0%)	212 (100.0%)
	Mammography				
	normal	59 (85.5%)	58 (80.6%)	64 (90.1%)	181 (85.6%)
	abnormal	1 (1.4%)	0 (0.0%)	2 (2.8%)	3 (1.4%)
	ND/UNK/NA	29 (42.0%)	34 (47.2%)	15 (21.1%)	76 (36.0%)

ND/UNK/NA = not done(ND) / unknown(UNK) / not applicable, not available, not assessable(NA)

Comments on mammography (if abnormal) by treatment, subject and visit

TREAT	SUBJECT	full analysis protocol set	Per set	Timepoint	Mammography	Date of Last Mammography	Mammography (text)
2M P 604 2M / 2M P 604 PC	25	yes	no	Final	abnormal	29JUN00	calcification in left breast
2M P 604 2M / 2M P 604 PD	73	yes	no	Screening	abnormal	08FEB00 08FEB00	bilateral/fatty involution (without pathological changes) and in left breast small benign densities (small cysts?)
2M P 604 PC / 2M P 604 PD	6	yes	no	Final	abnormal	29AUG00	density on right side
	15	yes	yes	Final	abnormal	18SEP00	tumor naxxa ext.
	57	yes	no	Final	ND/UNK/NA		mammography done in March 2000

Further description of mammography (if normal) by treatment and visit

Timepoint		2M P 604 2M	2M P 604 2M	2M P 604 PC	Overall
		/ 2M P 604 PC	/ 2M P 604 PD	/ 2M P 604 PD	
Screening	Number of patients	69 (100.0%)	50 (100.0%)	51 (100.0%)	169 (100.0%)
	Symptom / Diagnosis				
	fibroadenoma	48 (74.1%)	39 (78.0%)	27 (72.5%)	119 (70.4%)
	fatty involution	7 (12.1%)	5 (10.0%)	6 (15.7%)	17 (10.1%)
	other	3 (5.8%)	16 (32.0%)	9 (23.8%)	28 (16.5%)
Final	Number of patients	69 (100.0%)	51 (100.0%)	58 (100.0%)	169 (100.0%)
	Symptom / Diagnosis				
	fibroadenoma	29 (42.0%)	29 (56.9%)	26 (48.3%)	83 (49.0%)
	fatty involution	0 (0.0%)	1 (2.0%)	2 (3.4%)	4 (2.4%)
	other	4 (5.8%)	1 (2.0%)	1 (1.7%)	6 (3.6%)

Table 13. Cervical Cytology (Study Report, page 1363)

Cervical smear by treatment and visit

Timepoint		SH P 604 DM / SH P 604 PD	SH P 604 DM / SH P 604 PD	SH P 604 PC / SH P 604 PD	Overall
Screening	Number of patients	69 (100.0%)	72 (100.0%)	71 (100.0%)	212 (100.0%)
	Cytological Smear				
	CI/CII	69 (100.0%)	71 (98.6%)	70 (98.6%)	210 (99.1%)
	≥CIII	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ND/UNK/NA	0 (0.0%)	1 (1.4%)	1 (1.4%)	2 (0.9%)
Final	Number of patients	69 (100.0%)	72 (100.0%)	71 (100.0%)	212 (100.0%)
	Cytological Smear				
	CI/CII	46 (66.5%)	50 (69.4%)	61 (85.9%)	159 (75.0%)
	≥CIII	1 (1.4%)	2 (2.8%)	0 (0.0%)	3 (1.4%)
	ND/UNK/NA	20 (29.0%)	20 (27.8%)	10 (14.1%)	50 (23.6%)

ND/UNK/NA = not done(ND) / unknown(UNK) / not applicable,not available,not assessable(NA)

Abnormal cervical smear by treatment, subject and visit

TREAT	SUBJECT	Full analysis set	Per protocol set	Timepoint	Cytological Smear	Date of Cytological Smear	Cytological Smear (text)
SH P 604 DM / SH P 604 PD	112	yes	no	Final	≥CIII	04JUL02	epithelial dysplasia
SH P 604 DM / SH P 604 PD	252	yes	no	Final	≥CIII	21MAR01	atypical cells
	273	yes	yes	Final	≥CIII	04OCT01	cervical dysplasia

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Table 14. Endometrial Biopsies and Transvaginal Ultrasound
 (Study Report, pages 160-161)

Summary of the results of the central reading of endometrial biopsies and transvaginal ultrasound at Last Visit

Central reading	EM		DM		Placebo		Overall	
	n	%	n	%	n	%	n	%
Result available	34		45		47		126	
Inadequate for assessment (insufficient tissue)	14	41.2	11	24.4	20	42.6	45	35.7
TVU information: ≤ 5 mm	14	41.2	11	24.4	19	40.4	44	34.9
> 5 mm	0	0	0	0	1	2.1	1	0.8
Atrophic	14	41.2	23	51.1	26	55.3	63	50.0
Proliferative	3	8.8	2	4.4	0	0	5	4.0
Polyps	0	0	0	0	1	2.1	1	0.8
Progestational secretory	2	5.9	8	17.8	0	0	10	7.9
Menstrual	1	2.9	1	2.2	0	0	2	1.6

TVU = transvaginal ultrasonography, n = number of patients

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Table 1 FDA-Approved Estrogen and Estrogen-Progestin Products for the Prevention of Postmenopausal Osteoporosis

Product	Active Ingredients	Doses (mg)
Estrogen		
Premarin®	conjugated equine estrogens	0.3, 0.45, 0.625, 0.9, 1.25, 2.5
Estrace®	estradiol	0.5, 1.0, 2.0
Climara® (transdermal)	estradiol	0.025, 0.05, 0.075, 0.1
Menostar™ (transdermal)	estradiol	0.014
Ogen®	estropipate	0.75, 1.5, 3.0
Ortho-Est®	estropipate	0.75
Vivelle-Dot® (transdermal)	estradiol	0.025, 0.0375, 0.05, 0.075, 0.1
Estrogen/Progestin		
Prempro™	conjugated equine estrogens/ medroxyprogesterone acetate	0.625/2.5 0.625/5.0 0.45/1.5 0.3/1.5
Premphase®		0.625 x 14 days; 0.625/5.0 x 14 days
Activella®	estradiol/norethindrone acetate	1.0/0.5
Femhrt®	ethinyl estradiol/norethindrone acetate	0.005/1.0
Ortho-Prefest™	estradiol/norgestimate	1.0/0.09

Table 2. Main Results of Women's Health Initiative Estrogen-Progestin Trial

Outcomes	No. of Patients (Annualized %)		Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)			
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	NA	NA	NA
Cardiovascular disease†					
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PICA	163 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.88-2.31
Fatal	18 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.30	1.08-2.08	0.83-2.70
Venous thromboembolic disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.25-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total cardiovascular disease	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.00-1.49
Cancer					
Invasive breast	166 (0.38)	124 (0.30)	1.26	1.00-1.59	0.83-1.92
Endometrial	22 (0.05)	25 (0.06)	0.83	0.47-1.47	0.29-2.32
Colorectal	45 (0.10)	67 (0.16)	0.83	0.43-0.92	0.32-1.24
Total	502 (1.14)	458 (1.11)	1.03	0.90-1.17	0.86-1.22
Fractures					
Hip	44 (0.10)	62 (0.15)	0.66	0.45-0.98	0.33-1.33
Vertebral	41 (0.09)	60 (0.15)	0.66	0.44-0.96	0.32-1.34
Other osteoporotic	579 (1.31)	701 (1.70)	0.77	0.69-0.86	0.63-0.94
Total	650 (1.47)	768 (1.91)	0.76	0.69-0.85	0.63-0.92
Death					
Due to other causes	165 (0.37)	166 (0.40)	0.92	0.74-1.14	0.62-1.35
Total	231 (0.52)	218 (0.53)	0.96	0.82-1.18	0.70-1.37
Global index‡	751 (1.70)	623 (1.51)	1.15	1.03-1.28	0.95-1.39

CI indicates confidence interval; NA, not applicable; CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PICA, percutaneous transluminal coronary angioplasty.
 †CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 8 silent MIs. Total cardiovascular disease is limited to events during hospitalization except venous thromboembolic disease reported after January 1, 2000.
 ‡Other osteoporotic fractures include all fractures other than chest/sternum, skull/face, fingers, toes, and cervical vertebrae, as well as hip and vertebral fractures reported separately.

Table 3. Main Results of Women's Health Initiative Estrogen-alone Trial

Table 3. Clinical Outcomes by Randomization Assignment

Outcomes	No. of Patients (Annualized %)		Hazard Ratio*	Nominal 95% CI	Adjusted 95% CI
	CEE (n = 5310)	Placebo (n = 5420)			
Follow-up time, mean (SD), mo	81.6 (19.3)	81.9 (19.7)	NA	NA	NA
Cardiovascular disease†					
CHD	177 (0.49)	199 (0.54)	0.91	0.75-1.12	0.72-1.15
CHD death	54 (0.15)	59 (0.16)	0.94	0.65-1.36	0.64-1.63
Nonfatal MI	132 (0.37)	153 (0.41)	0.89	0.70-1.12	0.63-1.26
Stroke	158 (0.44)	118 (0.32)	1.36	1.10-1.77	0.97-1.99
Fatal	15 (0.04)	14 (0.04)	1.13	0.54-2.34	0.38-3.36
Nonfatal	114 (0.32)	85 (0.23)	1.39	1.05-1.84	0.91-2.12
Venous thromboembolic disease	101 (0.28)	78 (0.21)	1.33	0.99-1.79	0.86-2.08
Deep vein thrombosis	77 (0.21)	54 (0.15)	1.47	1.04-2.08	0.87-2.47
Pulmonary embolism	49 (0.13)	37 (0.10)	1.34	0.87-2.05	0.70-2.55
Total cardiovascular disease	311 (2.25)	246 (2.01)	1.12	1.01-1.24	0.97-1.30
Cancer					
Invasive breast	94 (0.26)	124 (0.33)	0.77	0.59-1.01	0.57-1.06
Colorectal	61 (0.17)	58 (0.16)	1.08	0.75-1.55	0.63-1.96
Total	372 (1.03)	403 (1.10)	0.93	0.81-1.07	0.75-1.16
Fractures					
Hip	38 (0.11)	64 (0.17)	0.61	0.41-0.91	0.33-1.11
Vertebral	39 (0.11)	64 (0.17)	0.62	0.42-0.93	0.34-1.13
Total	603 (1.39)	724 (1.95)	0.70	0.63-0.79	0.59-0.83
Death					
Due to other causes‡	193 (0.53)	185 (0.50)	1.08	0.88-1.32	0.79-1.46
Total	291 (0.81)	289 (0.78)	1.04	0.88-1.22	0.81-1.32
Global index§	692 (1.92)	705 (1.90)	1.01	0.91-1.12	0.89-1.14

Abbreviations: CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; NA, not applicable.
 *From Cox proportional hazards model stratified by age, prior disease, and randomization status in the dietary modification trial.
 †CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 14 silent MIs. Total cardiovascular disease is limited to events requiring or during hospitalization except venous thromboembolic disease reported after January 1, 2000.
 ‡All deaths except those from breast or colorectal cancer, definite/probable CHD, pulmonary embolism, or cerebrovascular disease.
 §The global index represents the first event for each participant from among the following: CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fracture, or death due to other causes.

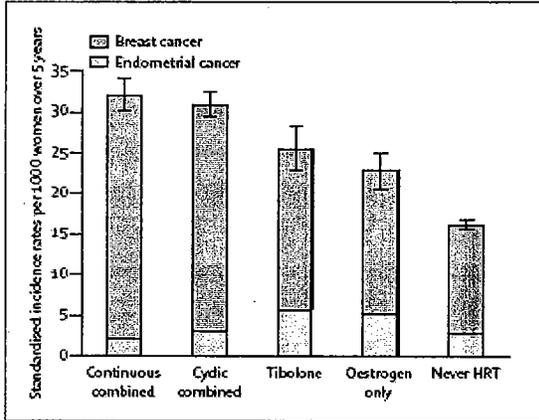
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Figure 2. Incidence of Breast and Endometrial Cancer for Women Reporting Use of Different Hormone Replacement Regimens in the Million Women Study



Standardized incidence rates for endometrial and breast cancer per 1000 women in the study cohort over a 5-year period, for current users of various types of HRT at recruitment and for never users of HRT. Error bars are 95% confidence intervals. Incidence rates were calculated by taking never-users of HRT as the standard and standardizing by age, region of residence, socioeconomic status, time since menopause, parity, use of oral contraceptives, body-mass index, and alcohol consumption. (Reference 4, Figure 6)

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