Efficacy and Tolerability of a Novel Estradiol Vaginal Ring for Relief of Menopausal Symptoms

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OBJECTIVE: To assess the efficacy, tolerability, and acceptance of a vaginal ring delivering the equivalent of 50 or 100 μg per day of estradiol (E2), compared with placebo, for relief of moderate to severe vasomotor symptoms and urogenital symptoms in postmenopausal women.

METHODS: Women with moderate to severe vasomotor symptoms (seven or more per day or 56 per week average) received 13 weeks of treatment with a vaginal ring delivering 50 μg per day E2 ($n = 113$) or 100 μg per day E2 ($n = 112$), or a placebo vaginal ring ($n = 108$). Severity of vasomotor symptoms was assessed by a daily diary card and the Greene Climacteric Scale. Urogenital signs and symptoms were evaluated via patient and physician assessment and vaginal cytology. Participant satisfaction with the vaginal ring was evaluated via questionnaire.

RESULTS: Vasomotor symptoms significantly improved in both treatment groups, compared with placebo ($P < .05$). There was a trend toward greater improvement in patient assessment of urogenital signs with active rings compared with placebo. For women with vaginal atrophy at baseline ($n = 60$), the maturation index improved significantly in both treatment groups compared with placebo. Total Greene Climacteric Scale scores significantly improved for both E2 vaginal ring groups ($P < .05$) compared with placebo. The vaginal rings were well tolerated. Most adverse events were mild or moderate and consistent with estrogen therapy.

CONCLUSION: A novel vaginal ring delivering the equivalent of 50 or 100 μg per day of E2 significantly reduced the number and severity of vasomotor symptoms and improved urogenital symptoms, compared with placebo. The E2 vaginal ring was well tolerated. (Obstet Gynecol 2003; 102:823–34. © 2003 by The American College of Obstetricians and Gynecologists.)

Although oral and transdermal estrogen replacement therapy (ERT) is indicated for the treatment of both systemic vasomotor and urogenital symptoms of menopause, many women require the addition of local therapy to achieve adequate control of vaginal atrophy and related symptoms, such as vaginal dryness and irritation, incontinence, and pain during intercourse.[1] In addition, most transdermal delivery systems require frequent patch changes, and some women experience skin irritation with their use.[2] Overall, more than half of all women who begin hormone replacement therapy (HRT) with oral or transdermal products discontinue treatment within the first year.[3]

Local ERTs currently available include vaginal creams and tablets and a low-dose estradiol (E2) vaginal ring. Many women find vaginal creams and tablets to be messy and inconvenient, and compliance with these regimens is often poor.[4,5] Furthermore, the currently available local estrogen preparations, including the low-dose E2 vaginal ring, do not deliver sufficient estrogen to effectively treat vasomotor symptoms and are indicated only for the treatment of local urogenital symptoms.[4,6–8]

A novel vaginal ring approved in 2001 for use in the United Kingdom is designed to allow the treatment of both vasomotor and urogenital menopausal symptoms. This E2 vaginal ring has a central core surrounded by a drug-free, rate-controlling membrane that ensures continuous, controlled release of E2 acetate at a rate equivalent to 50 μg per day or 100 μg per day of E2 for 3 months. Estradiol acetate is hydrolyzed rapidly after release from the vaginal ring to the naturally occurring hormone E2. In pharmacokinetic studies in healthy, postmenopausal women, the vaginal ring delivering 50 μg per day E2 and the vaginal ring delivering 100 μg per day E2 achieved mean daily serum concentrations of E2 of 150–280 pmol/L (41–76 pg/mL).[9] This is consistent

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with serum E2 levels of other nonoral ERTs that have been shown to be effective in treating the systemic and urogenital signs and symptoms of menopause. For instance, in matrix-type transdermal patches aimed to deliver 25 μg, 50 μg, or 100 μg per day, mean steady-state concentrations of E2 are approximately 110–147 pmol/L (30–40 pg/mL).[2] Repeated daily administration of 2 mg oral micronized E2 results in E2 levels between 294 and 551 pmol/L (80–150 pg/mL) for several hours after dosing; after 24 hours, E2 levels are greater than 147–184 pmol/L (40–50 pg/mL).[2] With the low-dose, 7.5-μg-per-day E2-releasing vaginal ring (Estring, Pharmacia & Upjohn, Kalamazoo, Michigan), average steady-state concentrations have been reported at 21 and 28 pmol/L (5.7 and 7.6 pg/mL).[10]

Vaginal delivery of E2 overcomes many of the disadvantages of other forms of ERT. For example, an E2 vaginal ring eliminates the daily or weekly dosing routines associated with oral or transdermal therapy; insertion of a ring only once every 3 months might lead to improved compliance because of its convenience. Vaginal delivery also avoids the first-pass metabolism and inactivation by hepatic enzymes, which affects oral E2, thereby possibly reducing unwanted side effects.[2,6] In addition, 10–25% of women taking oral therapy still experience urogenital symptoms, even when their vasomotor symptoms are adequately controlled.[1,11] The E2 vaginal ring is discreet and convenient, delivering E2 directly to the vaginal tissues to relieve urogenital symptoms, as well as giving steady serum levels that effectively relieve vasomotor symptoms. With this in mind, a comparative study has shown that a vaginal ring has greater patient acceptance than a vaginal cream, with 64% of women preferring the vaginal ring compared with only 18% preferring the vaginal cream.[6]

The phase III trial reported herein assessed the efficacy, tolerability, and participant satisfaction with a vaginal ring delivering the equivalent of either 50 μg per day or 100 μg per day of E2 for the treatment of moderate to severe vasomotor symptoms and signs of urogenital atrophy associated with menopause.

MATERIALS AND METHODS

This double-blind, randomized, placebo-controlled trial was conducted at 35 sites in the United States. Healthy postmenopausal women were treated for 13 weeks with a vaginal ring delivering the equivalent of either 50 μg per day E2 or 100 μg per day E2, or a placebo vaginal ring. The active vaginal ring (Femring, Galen Holdings, PLC, Craigavon, United Kingdom) contains E2 acetate in a reservoir system within the ring polymer, which is released steadily over 3 months.

At the screening visit, demographic data, medical history, and prior and concomitant medication were recorded for each potential study participant. Screening visit assessments included physical examination with urine pregnancy test, vital signs and weight, hematology, and biochemistry; mammography; vaginal examination for signs of vaginal atrophy (pallor, petechiae, dryness, friability, atrophy); endometrial biopsy for women with an intact uterus; and vaginal cell maturation index (maturation index = 0.2 × percent parabasal cells + 0.6 × percent intermediate cells + 1.0 × percent superficial cells). For the maturation index, vaginal atrophy at baseline was defined as a score of 52 or less.[12,13] A central laboratory calculated the maturation index. All potential participants in the study recorded the frequency and severity of moderate to severe vasomotor symptoms on a daily diary card during the 2-week period between the screening visit and randomization.

A postmenopausal woman, with or without a uterus, was eligible for enrollment in this study if she had had at least seven moderate to severe hot flushes per day or an average of at least 56 moderate to severe vasomotor symptoms per week for the 2 weeks before randomization. In addition, a woman with a uterus was required to have had amenorrhea for more than 12 months before randomization; if she had amenorrhea for less than 12 but at least 6 months, she was also required to have a follicle-stimulating hormone level of at least 40 IU and an E2 level of no more than 20 pg/mL. A woman was also eligible if she had had a hysterectomy and bilateral oophorectomy performed more than 6 weeks before randomization. Finally, a woman who had had a hysterectomy without bilateral oophorectomy was eligible if she had a follicle-stimulating hormone level of at least 40 IU and an E2 level of no more than 20 pg/mL. The enrollment period for the study was 12 months.

Exclusion criteria included past or current thromboembolic disorder, or cerebrovascular accident; endometriosis; allergy or intolerance to previous ERT or HRT, including disabling breakthrough bleeding; past or current estrogen-dependent neoplasia; abnormal uninvestigated vaginal bleeding within 6 months of randomization; and known or suspected pregnancy. Previous treatment with any of the following was also reason for exclusion: estrogen, progestogen, androgen, or systemic corticosteroids by the oral route within 8 weeks of screening, by transdermal or buccal delivery within 4 weeks of screening, or by injection within 6 months of screening; hormone pellets or implants inserted within the previous 5 years or an implant removed within the past 3 months; unopposed ERT for 6 months or more in women with an intact uterus; or selective estrogen receptor modulators within 8 weeks of screening.

The protocol and informed consent form were reviewed by either the institutional review board for the individual study site or a central institutional review board, and written informed consent was obtained from all patients at the screening visit. A randomization schedule was generated with the SAS Proc Plan (SAS Institute, Cary, NC). Women who met the inclusion and exclusion criteria were randomized in blocks of six to 13 weeks of treatment with a vaginal ring delivering the equivalent of 50 μg per day or 100 μg per day E2 or a placebo vaginal ring. Women with an intact uterus who received study treatment for at least 4 weeks were given 2.5 mg per day oral norethindrone or 10 mg per day oral medroxyprogesterone acetate (at the discretion of the investigator) for 14 days after removal of the vaginal ring.

Each participant was instructed to complete a daily diary card to record the number and severity of hot flushes and to return to the study site for the following evaluations at weeks 4, 8, and 13: patient assessment of urogenital symptoms and vaginal ring acceptability, Greene Climacteric Scale scores, and review of patient diary cards. In addition, vital signs and weight, adverse events, and prior and concomitant medications were recorded. Additional assessments at week 13 included physical examination, vaginal examination and vaginal pH, vaginal cytology and maturation index, and hematology and biochemistry.

Colposcopic examinations were performed in addition to all other investigations in a substudy conducted at four sites. A total of 45 consecutive women were randomly assigned to one of the three treatment groups (E2 vaginal ring 50 μg per day, $n = 15$; E2 vaginal ring 100 μg per day, $n = 16$; placebo, $n = 14$) and underwent colposcopic examinations at baseline and at weeks 4 and 13 for evaluation of changes to the vaginal epithelium.

The primary efficacy variable was the frequency and severity of moderate to severe vasomotor symptoms, as recorded on daily diary cards with a 4-point scale (0–3, in which 0 = no flushes, 1 = mild, 2 = moderate, and 3 = severe). For the urogenital efficacy variables, the investigators evaluated vaginal atrophy, pallor, vaginal dryness, and friability at each vaginal examination according to a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Participants used a questionnaire to evaluate vaginal dryness, irritation, or itching; difficulty passing urine, urine frequency, and urine leakage; and pain during intercourse, pain after intercourse, and bleeding after intercourse according to the following 4-point scale: 0 = not at all, 1 = a little, 2 = quite a bit, and 3 = extremely.

Information on vasomotor symptoms and other climacteric symptoms was also recorded according to the Greene Climacteric Scale, a validated menopausal symptom scale with a score range of 0 to 63. Higher scores indicate greater numbers of symptoms, greater severity of symptoms, or both.[14]

At every scheduled treatment visit, each participant completed a ring acceptability questionnaire to summarize her experiences with and opinions about the vaginal ring. Questions addressed whether the ring caused discomfort for the woman or her partner, the ease of ring removal and insertion, and the woman's willingness to use the product or recommend the product to a friend. All questions were answered as "yes," "no," or "N/A" (not applicable).

The primary efficacy analysis was based on a modified intent-to-treat population, which included all randomized participants with a baseline measurement of moderate to severe vasomotor symptoms who had a vaginal ring inserted and who had at least one moderate to severe vasomotor symptoms evaluation during the study. The primary end point was the mean change in the number of moderate to severe vasomotor symptoms from baseline to weeks 4, 8, and 12, with last observation carried forward. (Although the study was designed as a 13-week trial, the moderate to severe vasomotor symptoms analysis was done at week 12 to accommodate a request from the US Food and Drug Administration.) The analysis compared each active treatment group with the placebo group by two-way analysis of variance, with treatment group and study center as factors, and Dunnett two-sided test with 95% confidence intervals adjusted for multiple pairwise comparisons.[15] Dunnet two-sided test for many-to-one comparisons was used at the request of the US Food and Drug Administration. Two-tailed tests were used at a significance level of $\alpha = .05$.

Based on previous unpublished studies of this E2 vaginal ring, mean reductions from baseline in weekly moderate to severe vasomotor symptoms of 37 for the placebo and 64 and 71 for the 50-μg and 100-μg vaginal rings, respectively, were assumed. The standard deviation of these numbers was assumed to be 30 in all treatment groups. Based on these assumptions, 85 women per group would have been sufficient to detect a difference as small as 13 moderate to severe vasomotor symptoms per week, with a power of 0.80 ($\beta = 0.20$) and an $\alpha = .05$. To account for dropouts, 115 women were to be randomized to each treatment arm. Because the discontinuation rate was actually less than predicted, enrollment was terminated early after 333 women were randomized.

In addition, within-treatment-group comparisons were performed to test the significance of the mean change at each week of treatment. The mean percentage reduction and the mean change in severity of moderate

Table 1. Baseline Characteristics of the All-Randomized Population

Characteristic	Placebo (n = 108)	Estradiol 50 μg/day (n = 113)	Estradiol 100 μg/day (n = 112)	All subjects (n = 333)
Age (y)	50.7 ± 6.5	52.6 ± 8.3	51.8 ± 6.6	51.7 ± 7.2
Age range (y)	29–67	29–85	33–73	29–85
Race				
White	87 (81)	84 (74)	86 (77)	257 (77)
Black	12 (11)	15 (13)	14 (12)	41 (12)
Hispanic	9 (8)	11 (10)	10 (9)	30 (9)
Asian/Pacific Islander	0 (0)	1 (0.9)	1 (0.9)	2 (0.6)
Native American	0 (0)	1 (0.9)	1 (0.9)	2 (0.6)
Other	0 (0)	1 (0.9)	0 (0)	1 (0.3)
Body mass index (mean) (kg/m^2)	28	29	28	28
Alcohol drinks per day				
0	99 (92)	104 (92)	89 (80)	292 (88)
1	9 (8)	5 (4)	18 (16)	32 (10)
2–4	0 (0)	4 (4)	5 (4)	9 (3)
Cigarettes per day				
0	89 (82)	90 (80)	91 (81)	270 (81)
1–6	2 (2)	7 (6)	6 (5)	15 (5)
7–12	16 (15)	13 (12)	12 (11)	41 (12)
>12	1 (0.9)	3 (3)	3 (3)	7 (2)
Menopausal status				
Naturally postmenopausal (>12 mo)	44 (41)	47 (42)	60 (54)	151 (45)
Naturally postmenopausal (>6–12 mo)	9 (8)	2 (2)	6 (5)	17 (5)
Surgically postmenopausal	37 (34)	39 (34)	27 (24)	103 (31)
Hysterectomized, ovaries intact	18 (17)	25 (22)	19 (17)	62 (19)
Sexually active*	51 (48)	61 (55)	59 (54)	171 (53)
Pain during intercourse†	25 (24)	19 (17)	24 (22)	68 (21)
Prior HRT use	85 (79)	95 (84)	81 (72)	261 (78)

HRT = hormone replacement therapy.

Data are presented as n (%) or mean ± standard deviation unless otherwise noted.

* Calculated from the number of women who, at study completion, answered yes or no to the question, "Did the ring cause discomfort for you during intercourse?"

† Modified intent-to-treat population.

to severe vasomotor symptoms were analyzed at each week of treatment with a two-way analysis of variance, with treatment group and study center as factors. The incidence of women showing 80% or more and 90% or more relief from moderate to severe vasomotor symptoms was analyzed with the Fisher exact test at each treatment week.

Changes in signs and symptoms of vaginal atrophy were analyzed for participants with signs and symptoms at baseline. A Cochran-Mantel-Haenszel test with site as a factor was used to adjust for any site effect in the analyses of the subjective assessment of vaginal symptoms and physician assessment of vaginal signs at the vaginal examination. A two-way analysis of variance was used to analyze the maturation index; for the purposes of statistical analysis, a maturation index of 52 or less was used to define the population with atrophy. Changes in Greene Climacteric Scale scores from baseline to weeks 4, 8, and 13 were analyzed with analysis of variance and analysis of covariance.

RESULTS

A total of 333 women were randomized: 113 to a vaginal ring delivering 50 μg per day E2 (50-μg group), 112 to a vaginal ring delivering 100 μg per day E2 (100-μg group), and 108 to a placebo vaginal ring. Baseline characteristics of the all-randomized population are shown in Table 1. More than half of the women (n = 168; 50.5%) had experienced natural menopause. The population also included 165 surgically postmenopausal women (49.5%), 62 of whom had intact ovaries. A total of 281 women (84%) were between age 40 and 60 years; 35 (10.5%) were 61–69 years old; 2 (0.6%) were aged 70 years or older; and 15 women (4.5%) were less than 40 years old. Eight women in the all-randomized population failed to provide any postbaseline data, and thus were not included in the modified intent-to-treat population, which consisted of 325 women: 111 in the E2 vaginal ring 50-μg group, 109 in the E2 vaginal ring 100-μg group, and 105 in the placebo vaginal ring group.

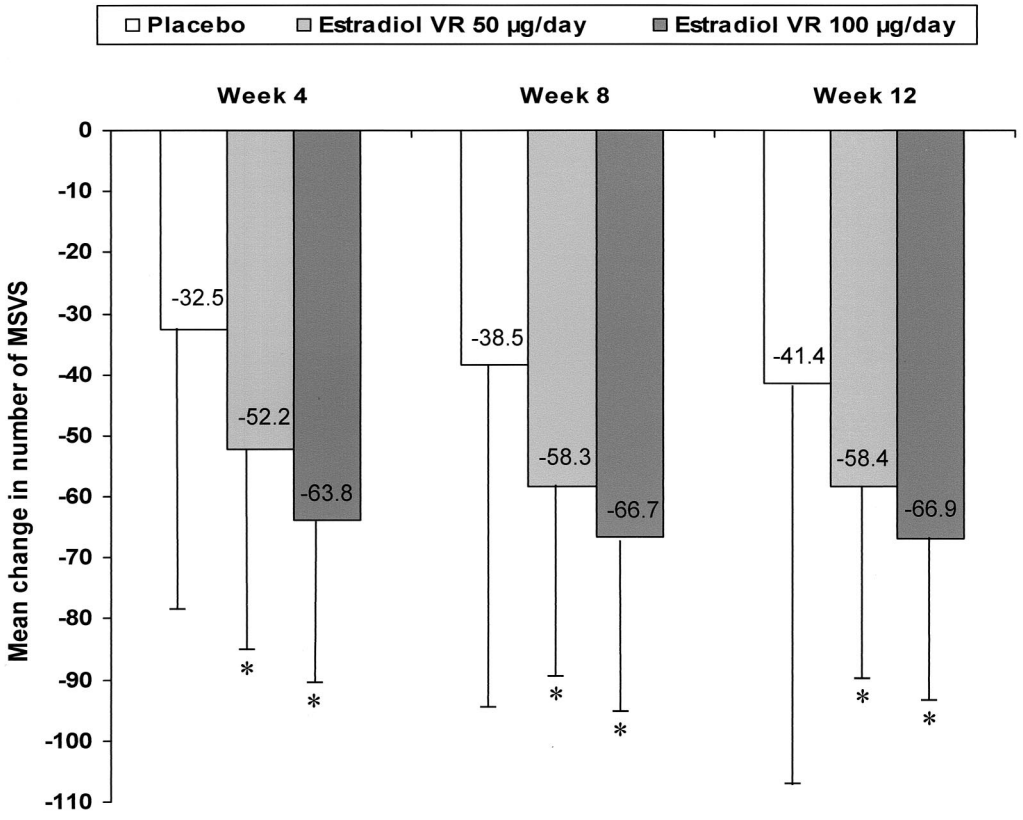

Figure 1. Mean change from baseline in the number of moderate to severe vasomotor symptoms per week, with last observation carried forward for the modified intent-to-treat population. *$P < .05$ vs placebo. MSVS = moderate to severe vasomotor symptoms; VR = vaginal ring.

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Overall, 279 participants (84%) completed the study. Fourteen women in the E2 vaginal ring 50-µg group (12.4%), 11 in the E2 vaginal ring 100-µg group (9.8%), and 29 in the placebo vaginal ring group (26.9%) discontinued treatment. Discontinuation rates were significantly lower in the E2 vaginal ring 50-µg and E2 vaginal ring 100-µg groups than in the placebo vaginal ring group ($P = .007$ and $P = .001$, respectively).

At baseline, there were no statistically significant differences among groups in the mean number of moderate to severe vasomotor symptoms per week (73.8 in the 50-µg group; 75.1 in the 100-µg group; 83.6 in the placebo group). The mean change from baseline in the number of moderate to severe vasomotor symptoms per week was significantly greater for both E2 vaginal ring groups compared with the placebo vaginal ring group at weeks 4, 8, and 12 ($P < .05$ for all comparisons). By week 12, the mean number of moderate to severe vasomotor symptoms per week in the placebo group was 42.2, compared with 15.5 in the E2 vaginal ring 50-µg and 8.3 in the 100-µg group (Figure 1).

Consistent with these results, the percentage reduction from baseline in the number of moderate to severe vasomotor symptoms per week was also significantly greater in the E2 vaginal ring 50-µg group than in the placebo vaginal ring group at weeks 2–13 ($P < .05$) and in the E2 vaginal ring 100-µg group than in the placebo vaginal ring group at all weeks ($P < .05$). By week 13, the percentage reductions from baseline in the number of moderate to severe vasomotor symptoms per week in the E2 vaginal ring 50-µg and 100-µg groups were 79.9% and 90.6%, respectively, compared with 49.1% in the placebo vaginal ring group ($P < .05$) (Figure 2).

Similarly, the percentage of participants with 90% or greater relief in the number of moderate to severe vasomotor symptoms per week was significantly greater in the E2 vaginal ring 50-µg group at each of weeks 2–13 ($P < .05$) and in the E2 vaginal ring 100-µg group at all 13 weeks of treatment ($P < .05$) compared with the placebo vaginal ring group. At the end of the study (week 13), 57.7%, 78.9%, and 25.7% of women in the E2 vaginal ring 50-µg, E2 vaginal ring 100-µg, and placebo vaginal

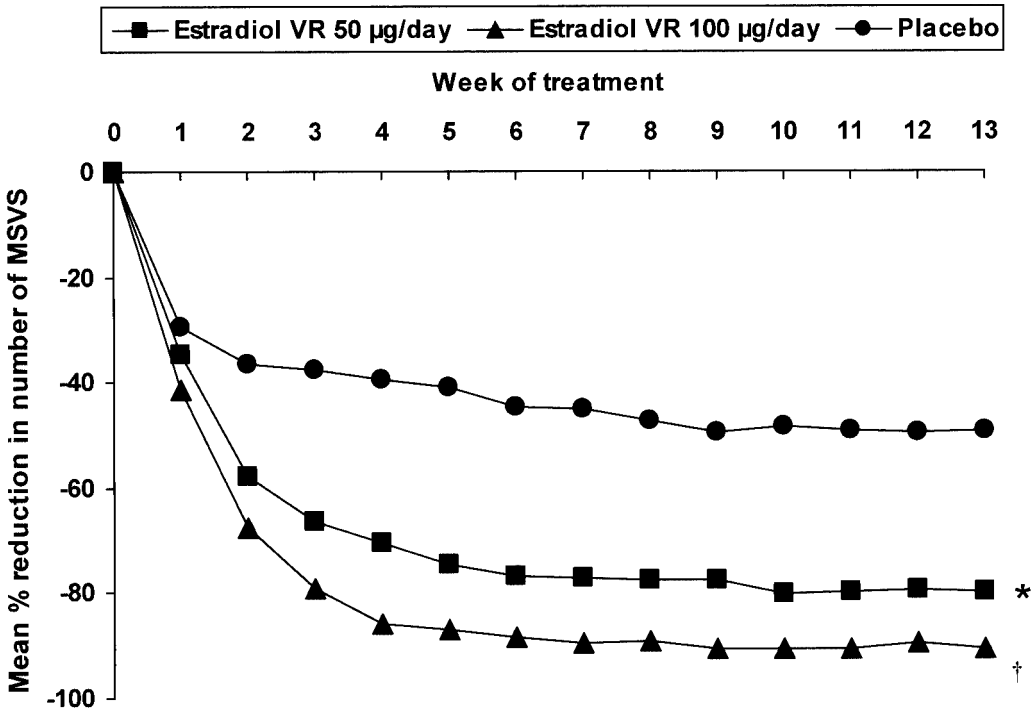

Figure 2. Mean percentage reduction from baseline in the number of moderate to severe vasomotor symptoms per week, with last observation carried forward for the modified intent-to-treat population. *$P < .05$ vs placebo at weeks 2 through 13. †$P < .05$ vs placebo at weeks 1 through 13. MSVS = moderate to severe vasomotor symptoms; VR = vaginal ring.
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ring groups, respectively, reported 90% or greater relief in the number of moderate to severe vasomotor symptoms per week.

Baseline mean scores for severity of moderate to severe vasomotor symptoms were comparable among the treatment groups, with scores of 2.46, 2.48, and 2.51 for the E2 vaginal ring 50-μg, E2 vaginal ring 100-μg, and placebo vaginal ring groups, respectively (median scores of 2.5 for all groups). The mean change from baseline in vasomotor symptom severity scores was significantly greater in both E2 vaginal ring groups than in the placebo vaginal ring group at weeks 4, 8, and 12 ($P < .05$) (Figure 3). Compared with the placebo vaginal ring group, the mean change from baseline in vasomotor symptom severity was significantly greater for the E2 vaginal ring 50-μg group at each of weeks 3–13 ($P < .05$) and for the E2 vaginal ring 100-μg group at all 13 weeks of treatment ($P < .05$). Furthermore, at week 12, 44 women in the E2 vaginal ring 50-μg group (40%), 63 women in the E2 vaginal ring 100-μg group (58%), 18 women in the placebo group (17%)–125 women overall (38%)–had reduced their vasomotor symptoms severity scores to 0.

The baseline mean severity of urogenital symptoms as assessed by the participants (Table 2) was comparable among the three groups with the exception of vaginal irritation or itching, which was significantly more severe in the placebo vaginal ring group (mean = 1.3; median = 1) than in the E2 vaginal ring 50-μg group (mean = 1.1; median = 1; $P < .05$), and vaginal dryness, which was significantly greater ($P = .025$) in the placebo vaginal ring group (mean = 1.0) and 100-μg group (mean = 1.1) than in the 50-μg group (mean = 0.8) (median for all groups = 1). There was a general trend toward greater improvement of urogenital symptoms in both E2 vaginal ring groups compared with the placebo vaginal ring group. Significant improvement in vaginal dryness was noted at weeks 4 and 8 for the E2 vaginal ring 100-μg group ($P < .05$). In addition, significant improvement in pain during intercourse was noted at week 4 in both E2 vaginal ring groups and at week 13 in the 100-μg group ($P \leq .05$ versus placebo).

A total of 60 women had vaginal atrophy at baseline as defined by the maturation index, with a mean maturation index of 30.6 in the placebo group ($n = 20$), 32.2 in the E2 vaginal ring 50-μg group ($n = 21$), and 29.6 in the

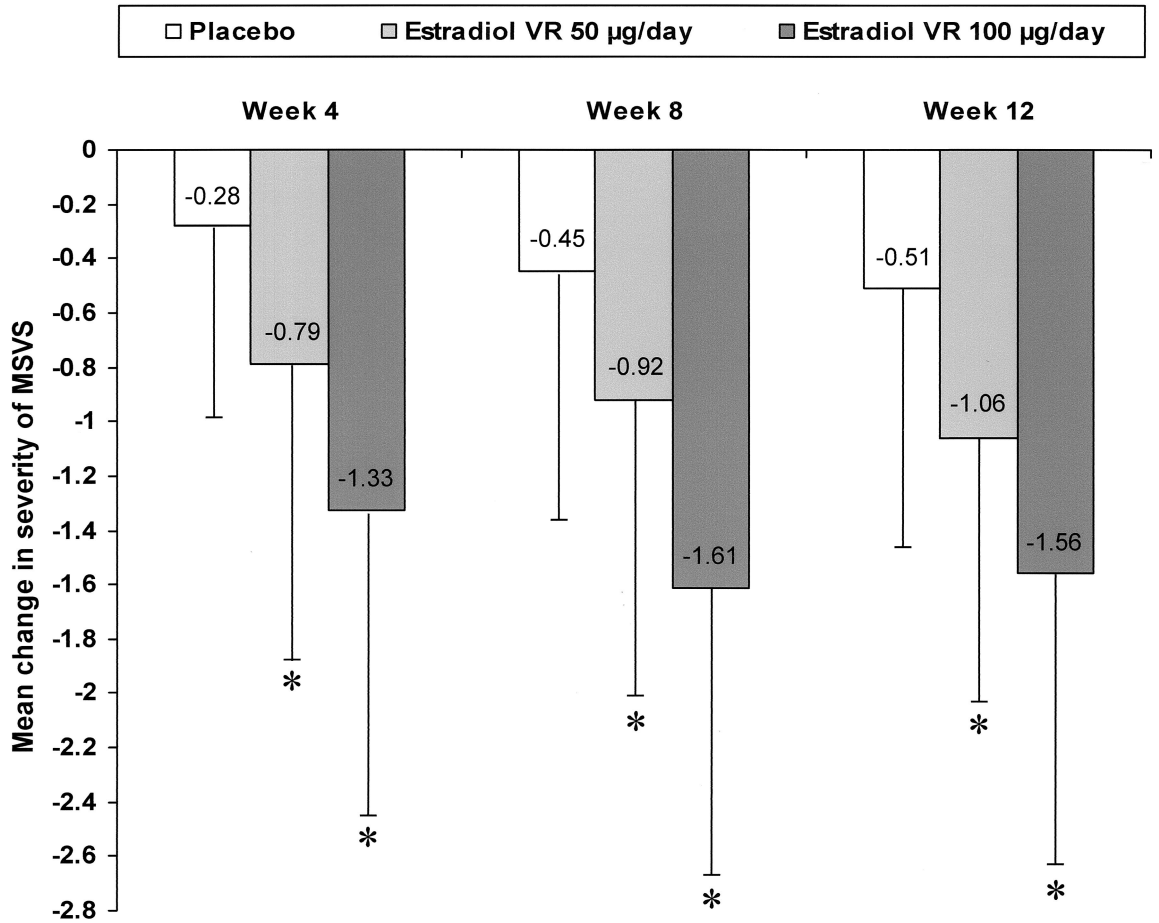

Figure 3. Mean change from baseline in severity of moderate to severe vasomotor symptoms, with last observation carried forward, modified intent-to-treat population.*$P < .05$ vs placebo. MSVS = moderate to severe vasomotor symptoms; VR = vaginal ring.

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E2 vaginal ring 100-μg group ($n = 19$). The mean change in maturation index from baseline to the final evaluation was significantly greater (ie, improved) with E2 vaginal ring 50 μg per day ($P = .008$) and 100 μg per day ($P = .003$) than with placebo vaginal ring (Figure 4). Based on the maturation index, none of the 21 women (0%) in the E2 vaginal ring 50-μg group and only 1 of the 19 women (5%) in the E2 100-μg group still had atrophy at the final evaluation, compared with 6 of 20 participants (30%) in the placebo group.

Physician assessment of urogenital signs of atrophy at week 13 revealed that vaginal atrophy and pallor were significantly improved in women with those signs at baseline in both E2 vaginal ring groups compared with the placebo vaginal ring group ($P < .001$). Vaginal dryness was significantly improved in the E2 vaginal ring 50-μg group ($P < .05$), and friability was significantly improved in the E2 vaginal ring 100-μg group compared with placebo vaginal ring ($P < .05$). Petechiae were improved in both active-treatment groups compared with placebo vaginal ring, but no statistically significant differences were noted (Figure 5). Overall, there was greater improvement in signs of vaginal atrophy among women with physician-diagnosed signs at baseline in the active-treatment groups than in the placebo vaginal ring group. Conversely, signs of vaginal atrophy were diagnosed as having worsened in more participants in the placebo vaginal ring group than in the active-treatment groups.

In the subset of 45 women who underwent colposcopy at baseline and at weeks 4 and 13, minor abnormalities consistent with sexual activity or the use of intravaginal products (eg, petechiae, ecchymosis, erythema, or peeling) were observed with comparable frequency across the three treatment groups. The expected lesions consistent with minor trauma, such as abrasions and erosions,

Table 2. Mean Change From Baseline in Severity of Urogenital Symptoms as Assessed by Participants*

Symptom	Placebo (n = 105)	Estradiol VR 50 μg/day (n = 111)	Estradiol VR 100 μg/day (n = 109)
Vaginal dryness (n)	60	58	70
Baseline	1.6	1.4	1.7
Week 4	−0.7	−0.9	−1.3†
Week 13	−0.8	−0.9	−1.3
Vaginal itching/ irritation (n)	32	35	29
Baseline	1.3	1.1†	1.2
Week 4	−0.6	−0.3	−0.6
Week 13	−0.8	−0.5	−0.4
Urinary frequency (n)	60	54	53
Baseline	1.5	1.5	1.6
Week 4	−0.6	−0.7	−0.8
Week 13	−0.7	−0.8	−1.0
Urinary leakage (n)	42	47	45
Baseline	1.3	1.3	1.4
Week 4	−0.5	−0.6	−0.7
Week 13	−0.4	−0.6	−0.5
Pain during intercourse (n)	25	19	24
Baseline	1.7	1.5	1.6
Week 4	−0.8	−1.1†	−1.2†
Week 13	−0.8	−1.2	−1.3†

VR = vaginal ring.

Bothered by symptom: 0 = not at all; 1 = a little; 2 = quite a bit; 3 = extremely. Score decrease indicates improvement.

* Last observation carried forward, modified intent-to-treat population.

† $P \leq .05$ vs placebo.

were noted more frequently in the placebo vaginal ring group. The number of women in this subset was too small for between-group statistical comparisons.

Baseline Greene Climacteric Scale scores were comparable across the three groups, with the exception of lower scores for the sexual dysfunction subscale in the two E2 vaginal ring groups. Total Greene Climacteric Scale scores and subscale scores were significantly lower (ie, improved) at weeks 4, 8, and 13 for both E2 vaginal ring groups than in the placebo vaginal ring group ($P < .05$ and $P < .002$, respectively). Table 3 shows the mean change from baseline in the overall Greene Climacteric Scale total score and subscale scores. No significant differences were observed between the two E2 vaginal ring groups in mean reductions in any subscale measure.

During the visits at weeks 4, 8, and 13, participants indicated that the vaginal rings were well tolerated. The vaginal ring was kept in place for the entire 13-week treatment period by 81%, 92%, and 84% of the women in the E2 vaginal ring 50-μg, E2 vaginal ring 100-μg, and placebo vaginal ring groups, respectively. Less than 25% of all women removed the vaginal ring during the 13-week treatment period, and most of those who did found the ring easy to remove and reinsert (Table 4). The reasons for removal of the vaginal ring were not captured in this study. Among the women who reported having sexual intercourse during the study period, the majority in all groups reported that the vaginal ring caused no discomfort to themselves or their partners. At

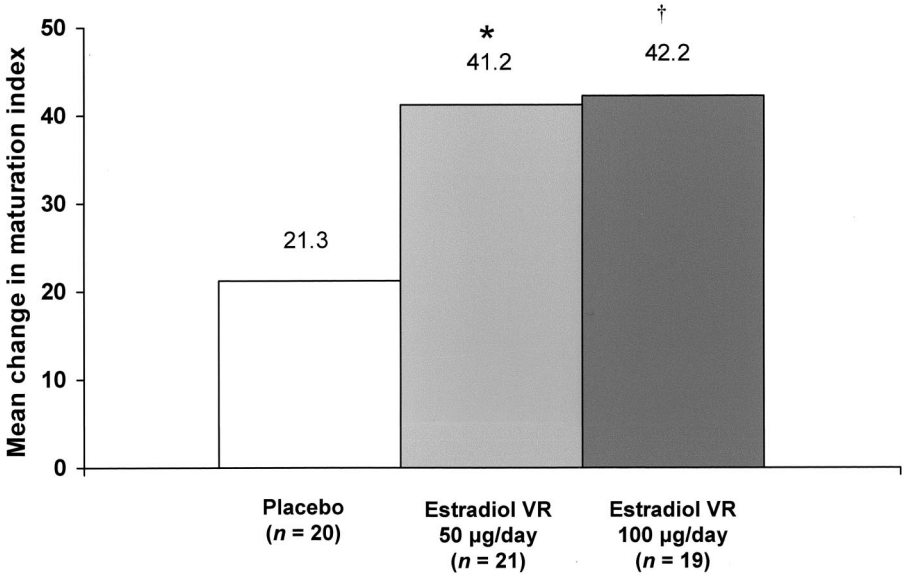

Figure 4. Mean change from baseline in maturation index for participants with vaginal atrophy at baseline by treatment group (modified intent-to-treat population). *P = .008 vs placebo. †P = .003 vs placebo. VR = vaginal ring.

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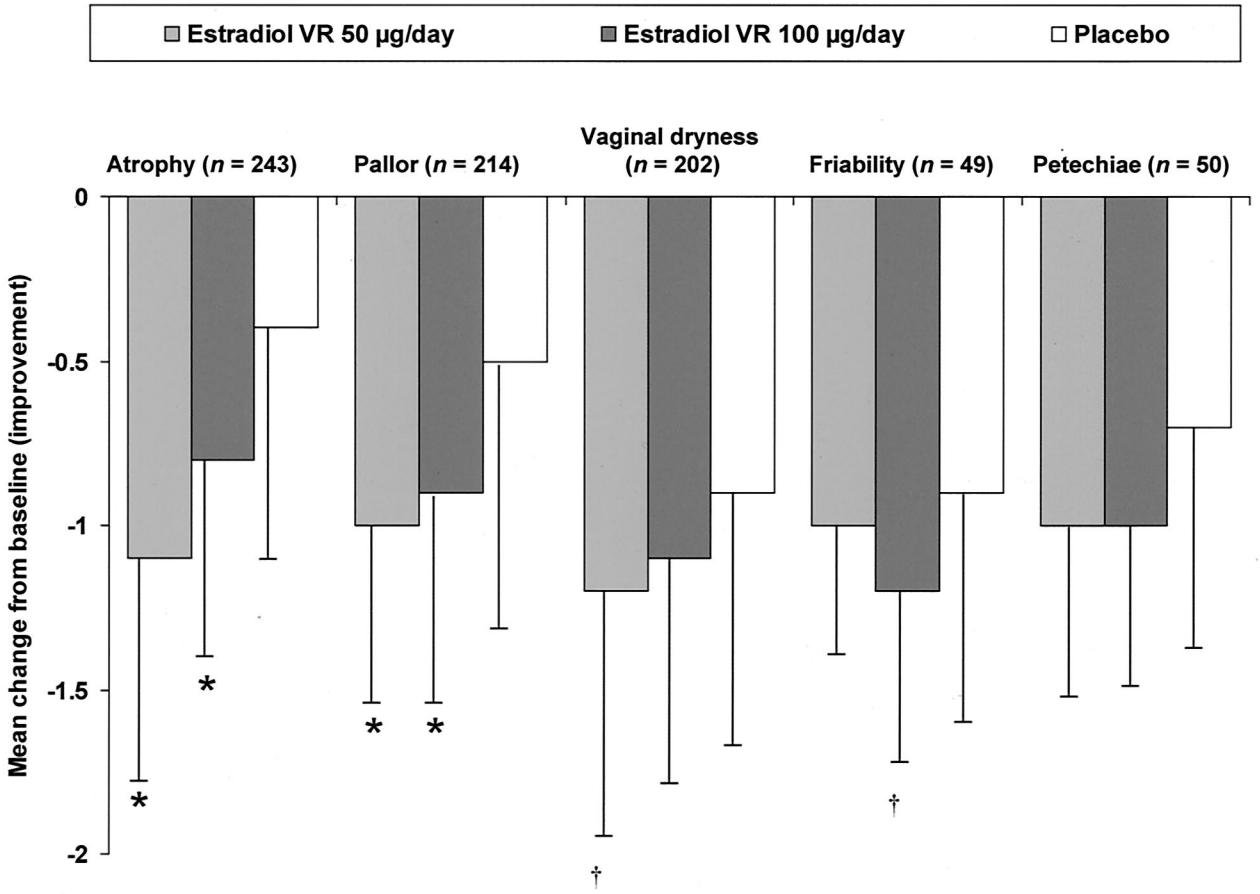

Figure 5. Change in vaginal atrophy measures at final assessment for participants with signs present at baseline. *$P < .001$ vs placebo. †$P < .05$ vs placebo. VR = vaginal ring.

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the end of the treatment period, 87% of the E2 vaginal ring 50-µg group and 92% of the 100-µg group indicated that they would use the vaginal ring for ERT if it were available, as did 80% of women in the placebo vaginal ring group ($P < .05$). Similarly, 93% and 99% of women in the E2 vaginal ring 50-µg and 100-µg groups, respec-

Table 3. Mean Change From Baseline in Greene Climacteric Scale Scores at Week 13 by Treatment Group*

	Estradiol VR 50 µg/day (n = 111)		Estradiol VR 100 µg/day (n = 109)		Placebo VR (n = 105)	
	Baseline	Change at week 13	Baseline	Change at week 13	Baseline	Change at week 13
Total score	18.44	−10.52†	17.80	−10.72†	20.96	−5.95
Subscale scores						
Psychological	8.81	−4.66†	8.45	−4.74†	10.16	−2.91
Anxiety	4.85	−2.56†	4.87	−2.86†	5.78	−1.94
Depression	3.97	−2.10†	3.58	−1.88†	4.38	−0.97
Somatic	3.40	−1.21†	3.39	−1.38†	4.39	−0.70
Sexual dysfunction	1.14	−0.72†	1.17	−0.69†	1.59	−0.56
Vasomotor	5.07	−3.68†	4.69	−3.66†	4.80	−1.61

VR = vaginal ring.
* Last observation carried forward, modified intent-to-treat population.
† $P < .002$ vs placebo.

Table 4. Subjective Assessment of Vaginal Ring Tolerability at Week 13

Tolerability parameter	Estradiol VR 50 μg/day (*n* = 111)		Estradiol VR 100 μg/day (*n* = 109)		Placebo VR (*n* = 105)	
	*n**	%	*n**	%	*n**	%
Ease of use						
Women who found VR easy to remove	15/21	71	14/16	88	10/10	100
Women who found VR easy to reinsert	19/21	90	13/13	100	10/10	100
Discomfort during intercourse						
Women who experienced discomfort	4/61	7	3/59	5	5/51	10
Partners who experienced discomfort	10/61	16	7/58	12	4/51	8
Overall satisfaction						
Women who would use VR for HRT if available	78/90	87	82/89	92†	55/69	80
Women who would recommend use of VR to a friend	84/90	93†	88/89	99†	56/69	81

VR = vaginal ring; HRT = hormone replacement therapy.
* Number of positive answers/total number of answers.
† $P < .05$ vs placebo.

tively, indicated that they would recommend the use of the vaginal ring to a friend, compared with 81% of women in the placebo vaginal ring group ($P < .05$).

The vaginal rings delivering the equivalent of 50 μg per day or 100 μg per day of E2 were generally well tolerated. The adverse events reported with the E2 vaginal rings were comparable to those reported with the placebo vaginal ring, with the exception of events expected to occur during ERT in postmenopausal women.

The most common adverse events in all three treatment groups in the all-randomized population ($n = 333$) were headache (8.7%), intermenstrual bleeding (vaginal bleeding among women with an intact uterus who were receiving active treatment) (6.6%), vaginal candidiasis (6.6%), and breast tenderness (6.3%). Most adverse events were mild or moderate in intensity, occurred more than 5 days after treatment onset, and were considered by the investigators to be definitely unrelated or probably unrelated to the study drug. No erosions were seen on routine gynecologic examinations in any women; colposcopy results revealed an erosion in one participant in the placebo group.

There were no notable differences among the treatment groups in laboratory values, vital signs, and physical examination parameters at any time during the study. No new clinically significant lesions were noted during pelvic examinations after treatment.

DISCUSSION

The results of this study show that a novel vaginal ring delivering 50 μg per day or 100 μg per day E2 provided adequate control of both systemic and urogenital menopausal signs and symptoms. The frequency and severity of vasomotor symptoms improved significantly in women in the active-treatment groups compared with placebo, with significantly more treated women gaining 90% or greater relief. Both the baseline frequency and improvement in vasomotor symptoms were similar to what have been seen in other studies of ERT.[16,17] Both total and all subscale Greene Climacteric Scale scores also improved significantly in the active-treatment groups.

Urogenital signs and symptoms, the secondary end point of the study, also showed improvement. The objective measures of urogenital atrophy, physicians' findings on vaginal examination, showed statistically significant improvements in all findings for active-treatment groups compared with placebo. When a different definition of atrophy, the maturation index, was used, resolution of atrophy was seen in all but one woman on active treatment. However, the maturation index also improved in 14 of 20 women in the placebo group. The mechanism for this improvement is unclear but has been previously noted in a study of the low-dose E2 vaginal ring.[18]

Subjective measures of symptoms all trended toward greater improvement in the active-treatment groups compared with placebo, and some differences compared with placebo were statistically significant. The improvement in urogenital symptoms occurred despite the relatively small number of women who noted symptoms at baseline and despite the use of a relatively insensitive 4-point scale. Together, these results demonstrate a generally beneficial effect of the E2 vaginal ring on urogenital atrophy. Overall, the findings of this study are similar to those of previous studies demonstrating the effectiveness of an E2 vaginal ring for improving postmenopausal vasomotor, urogenital, and other climacteric symptoms.[19,20]

The adverse events reported with the E2 vaginal rings were comparable to those reported with the placebo vaginal ring, except for events expected to occur during ERT in postmenopausal women. As expected, those adverse events usually associated with ERT occurred more frequently with the E2 vaginal rings than with placebo vaginal ring, yet the discontinuation rates due to adverse events were significantly lower in the E2 vaginal ring groups than in the placebo group.

As in previous reports, this novel E2 vaginal ring for relief of systemic as well as urogenital symptoms associated with menopause was well tolerated.[4,6,20] In one study, the ring was consistently in place at 12 weeks in 88% of the population.[21] In the present study, only a small proportion of women reported discomfort during intercourse, and the majority of women found the novel vaginal ring easy to remove and reinsert.

Notably, the population in this study was quite representative of the women seen in clinical practice. The mean age was 51.7 years; 84% were between 40 and 60 years; 50% were hysterectomized; and many already had symptoms of vulvovaginal atrophy even though they still had pronounced vasomotor symptoms.

This E2 vaginal ring offers a high degree of convenience and tolerability, which are key considerations in choosing a product for ERT. As a new option for women seeking relief of vasomotor and urogenital menopausal symptoms, this E2 vaginal ring can simplify hormone replacement regimens and improve treatment compliance.

In conclusion, postmenopausal women treated with a novel vaginal ring delivering E2 acetate at a rate equivalent to either 50 μg per day or 100 μg per day E2 experienced improved vasomotor and urogenital symptoms as measured objectively and subjectively.

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APPENDIX

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