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Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief

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ABSTRACT

Objective To evaluate the efficacy of two ultra-low-dose 17β-estradiol plus norethisterone acetate (NETA) treatment regimens for relieving menopausal symptoms.

Design A total of 577 postmenopausal women were enrolled, in three treatment groups in a double-blind, randomized, placebo-controlled study of 0.5 mg 17β-estradiol + 0.1 mg NETA or 0.5 mg 17β-estradiol + 0.25 mg NETA or placebo. Participants returned at weeks 4, 8, 12 and 24 for climacteric complaint evaluation based on a daily diary vasomotor symptom record. Patients were assessed by the Greene Climacteric Scale and urogenital symptoms were also evaluated.

Results Treatment with ultra-low-dose 0.5 mg 17β-estradiol + 0.1 mg NETA (0.1 Group) or 0.5 mg 17β-estradiol + 0.25 mg NETA (0.25 Group) effectively reduced the severity and number of hot flushes within the initial weeks of therapy. Compared to placebo, a rapid, statistically significant decrease in the frequency and severity of hot flushes was achieved by week 3, followed by further improvement which continued throughout the study. There were no statistically significant differences between the active treatment arms.

Conclusions The data show that both ultra-low-dose regimens are effective in reducing the severity and number of hot flushes compared to placebo, with good safety profiles.

INTRODUCTION

Used for more than five decades, hormone replacement therapy (HRT) is the most effective treatment for menopausal symptom relief[1]. The trend towards low-dose HRT began in the late 1990s with the introduction of the first low-dose, continuous combined preparation of 1 mg 17β-estradiol plus 0.5 mg norethisterone acetate (NETA). In 2002, controversial data from the Woman's Health Initiative (WHI)[2] accelerated interest in lower-dose formulations. The WHI

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used a relatively high-dose HRT regimen of 0.625 mg conjugated equine estrogens (CEE) combined with 2.5 mg medroxyprogesterone acetate (MPA). The study authors highlighted in the discussion that the results did not necessarily apply to other HRT formulations or lower dosages[2]. Furthermore, due to advanced age and lack of menopausal symptoms, the WHI study population did not represent the typical population treated with HRT.

Despite proven efficacy for menopausal symptom relief, the safety and risk/benefit profile of HRT has been the subject of debate in recent years as a result of the WHI study. Lowering the dose of HRT to reduce the incidence of side-effects (e.g. breast pain, bleeding), while still retaining the positive therapeutic effects, has become a key aim of treatment development in order to facilitate initiation and continuation of therapy[3–6]. Data also suggest that lower-dose formulations minimize risks such as venous thromboembolism and stroke[7–9]. Regulatory authorities, expert advisory bodies, menopause societies and many clinicians are increasingly recommending the use of the lowest effective dose of HRT[10–13].

The new data on dose-dependent side-effects and risks, along with well-established evidence, highlighted the need for further research into ultra-low-dose continuous combined (cc) HRT formulations. This paper is the first in a series of reports from the Clinical Study on Hormone Dose Optimisation in Climacteric Symptoms Evaluation (CHOICE) that evaluated the efficacy and safety of two different doses of ultra-low-dose ccHRT. A 24-week, randomized, double-blind, placebo-controlled, multinational study, it assessed ultra-low-dose ccHRT containing 0.5 mg 17β-estradiol plus 0.1 mg NETA (0.1 Group) and 0.5 mg 17β-estradiol plus 0.25 mg NETA (0.25 Group), compared to placebo, in postmenopausal women with moderate to severe vasomotor symptoms.

METHODS

Subjects

A total of 577 generally healthy, postmenopausal women, each with an intact uterus, between the ages of 44 and 65 years (mean age 55.5 years) were enrolled in the study. Of the 577 women, 575 took a study medication and 573 documented hot flushes in a daily diary. Table 1 outlines the demography of the trial population. Each subject was carefully screened to meet trial protocol requirements and informed consent was obtained before any trial-related activity and participation. Local Ethics Board approval of the protocol was obtained prior to the initiation of the study at each site, in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

Women were eligible to participate if they had at least 50 moderate to severe hot flushes per week, no menses during the past year or 6 months spontaneous amenorrhea with follicle stimulating hormone (FSH) levels >40 mIU/ml and estradiol levels <25 pg/ml. The same FSH and estradiol levels were used if the end of bleeding could not be determined due to previous HRT use. Additionally, each woman's endometrial thickness, as measured by transvaginal ultrasound, had to be <5.0 mm (double layer).

No women were allowed to enrol who had previous exposure to estrogen and/or progestogen HRT with oral therapy within 8 weeks, transdermal therapy, nasal spray and vaginal preparations within 4 weeks, injections within 6 months and implant removal within 4 weeks of the trial. Other factors that eliminated potential participants included known, suspected or previous history of breast cancer or estrogen-dependent neoplasia, as well as untreated endometrial hyperplasia and abnormal genital bleeding.

The study recruited generally healthy women. Thus, women were excluded if they had a history of diabetes mellitus, hypertension, any thromboembolic conditions and hepatic or renal impairment. Additional exclusion criteria were obesity (body mass index of greater than 35.0 kg/m^2), heavy smoking (>20 cigarettes per day), and a history of drug and alcohol abuse.

Study design

The CHOICE trial was a randomized, placebo-controlled, double-blind, multicenter, multinational, parallel-group evaluation with three treatment arms. Participants satisfying all entry criteria were randomly assigned to one of the three treatments (194 in 0.1 Group, 182 in 0.25 Group and 201 in placebo) for 24 weeks. Each participant was given a diary and asked to record daily the frequency and severity of hot flushes, other menopausal symptoms and the occurrence of spotting and bleeding. A single tablet of the assigned therapy was to be taken orally daily. Table 2 outlines the progression of the trial, providing details on which assessments were performed at each visit.

Table 1 Demography of trial population. Data are presented as mean ± standard deviation (SD) and range or as number (%)

	NETA 0.1 ($n = 194$)	*NETA 0.25* ($n = 181$)	*Placebo* ($n = 200$)	*All* ($n = 575$)
Age (years)				
Mean ± SD	55.2 ± 4.8	55.3 ± 4.4	56.1 ± 4.7	55.5 ± 4.6
Range	44.0–65.0	45.0–65.0	45.0–65.0	44.0–65.0
Race				
Caucasian	182 (94)	172 (95)	191 (96)	545 (95)
Asian/Pacific Islander	2 (1)	1 (1)	1 (1)	4 (1)
Black	0 (0)	2 (1)	0 (0)	2 (0)
Other	1 (1)	0 (0)	1 (1)	2 (0)
Not available	9 (5)	6 (3)	7 (4)	22 (4)
Body weight (kg)				
Mean ± SD	66.6 ± 10.1	68.6 ± 11.1	68.2 ± 10.3	67.8 ± 10.5
Range	45.0–94.1	46.8–101.5	46.2–105.0	45.0–105.0
Body mass index (kg/m^2)				
Mean ± SD	25.0 ± 3.6	25.4 ± 3.5	25.3 ± 3.6	25.3 ± 3.6
Range	16.7–35.4	17.4–36.6	17.5–35.1	16.7–36.6
Systolic blood pressure (mmHg)				
Mean ± SD	127.3 ± 14.9	127.7 ± 13.6	128.6 ± 13.5	127.8 ± 14.0
Range	95.0–162.0	80.0–159.0	80.0–158.0	80.0–162.0
Diastolic blood pressure (mmHg)				
Mean ± SD	78.2 ± 9.6	79.6 ± 8.4	79.6 ± 8.7	79.1 ± 9.0
Range	59.0–99.0	59.0–99.0	60.0–100.0	59.0–100.0
Smokers	30 (15)	39 (22)	35 (18)	104 (18)
Time since last menses				
≤1 year	31 (19)	29 (17)	31 (17)	91 (18)
>1–2 years	20 (12)	20 (12)	19 (11)	59 (12)
>2–5 years	46 (28)	40 (24)	39 (22)	125 (25)
>5–10 years	39 (23)	51 (31)	50 (28)	140 (27)
>10 years	30 (18)	26 (16)	39 (22)	95 (19)

Most subjects were Caucasian (95%) and had experienced their last menses between 2 and 10 years previously (71%). No notable differences in demographic characteristics were observed between treatment groups
NETA, norethisterone acetate

Efficacy assessment

The primary trial endpoint was change in the mean number of hot flushes. The severity of each flush was recorded by patients in their diary each day as 1 = mild (hot sensation without perspiration), 2 = moderate (hot sensation or flush with perspiration that does not interfere with daily activities), 3 = severe (hot sensations with perspiration that stops any present activity). A sensitivity analysis was performed, analyzing the mean changes in frequency and severity of moderate to severe hot flushes in order to validate results. At weeks 3, 4, 8, 12 and 24, the changes from baseline (week 0) for the ultra-low-dose 0.1 and 0.25 Groups were compared to the placebo group. To assess the severity score (SS), the following formula was used: SS = (2 × number of moderate flushes + 3 × number of severe flushes)/(number of moderate flushes + number of severe flushes). A significance level of 5% was used for all efficacy analyses.

Secondary endpoints were: hot flush weekly weighted score (HFWWS)[14], responses to the investigator-administered Greene Climacteric Scale[15], bleeding pattern[16], urogenital symptom score[17,18], vaginal maturation value and vaginal pH[17,18]. The HFWWS took into account the weekly number of hot flushes and their severity using the following formula: HFWWS = (number of mild hot

Table 2 Trial flow chart

	Pre-screening	*Screening*	*Baseline*	*Treatment*			
Visit number	−1	1	2	3	4	5	6
Week	−11 to −6	−3 to −2	0	4	8	12	24
Allowed time deviation (days)	–	–	–	±5	±7	±10	±14
Informed consent	X	X					
Inclusion/exclusion criteria		X	X				
Randomization			X				
Demographics		X					
Smoking habits		X					
Medical history		X					
Gynecological history		X					
History of ERT/HRT		X					
Vital signs		X	X	X	X	X	X
Height		X					
Physical examination		X					X
Gynecological examination		X					X
Cervical smear		X					X
Transvaginal ultrasound		X					X
Mammogram		X					
Follow-up mammogram							X
Estradiol, FSH, SHBG, IGF-1		X				X	X
TSH		X					X
Hematology and biochemistry		X				X	X
Lipid, glucose metabolism and hemostasis			X			X	X
Issue/review/collect diary cards		X	X	X	X	X	X
Greene Climacteric Scale			X	X	X	X	X
Urogenital symptoms			X			X	X
Vaginal smear			X			X	X
Vaginal pH			X			X	X
Concomitant illness		X					
Concomitant medication		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Drug dispensation			X	X	X	X	
Drug accountability			X	X	X	X	X
End of trial							X

ERT, estrogen replacement therapy; HRT, hormone replacement therapy; FSH, follicle stimulating hormone; SHBG, sex hormone binding globulin; IGF-1, insulin-like growth factor-1; TSH, thyroid stimulating hormone

flushes × 1) + (number of moderate hot flushes × 2) + (number of severe hot flushes × 3).

Using the Greene Climacteric Scale at visits 2–6, a total of 21 symptoms in three groups (psychological, somatic and vasomotor) were assessed and the severity of each symptom rated. In addition, sexual interest was also evaluated. Although urogenital difficulties, particularly atrophic vaginitis, are generally mild in a population of this age group, urogenital symptoms were analyzed at visits 2, 5 and 6. These included vaginal dryness, burning or itching, dyspareunia, dysuria and stress incontinence. Vaginal maturation values were assessed from vaginal smears and the vaginal pH checked by dipstick on visits 2, 5 and 6.

Statistical methodology

A closed testing procedure was adopted for the primary response variable for multiple treatment group comparison (to control the overall significance level of 0.05). An overall treatment group comparison for the three treatment groups (0.1, 0.25 and placebo) was performed based on the

Kruskal–Wallis test. If the overall test was statistically significant ($p < 0.05$), three pair-wise treatment comparisons were performed using a Wilcoxon test, stratified by country. Non-parametric test procedures were adopted because a Shapiro–Wilk test for normality was found to be significant. The primary efficacy analysis of the four co-primary endpoints (change from baseline to week 4 and week 12 in the number of moderate and severe hot flushes per week and the severity score of moderate and severe hot flushes per week) was performed by a Kruskal–Wallis test for the overall treatment comparison, and by a stratified Wilcoxon test, stratified by country, for the paired treatment comparisons. Estimated mean treatment differences and 95% two-sided confidence intervals were constructed for the differences between pairs of treatments (0.1 vs. placebo, 0.25 vs. placebo, and 0.1 vs. 0.25) at weeks 1 through 12 and 24. Both intention-to-treat (ITT) and per protocol (PP) analyses were conducted for the primary and secondary efficacy variables, except for bleeding and urogenital symptoms, where only ITT analysis was carried out. Missing values were replaced using the last-observation-carried-forward (LOCF) approach. The primary efficacy analysis was performed by an ANOVA model with treatment and center as fixed effects and the corresponding number of moderate to severe hot flushes per week in the run-in period as covariate.

RESULTS

Baseline characteristics for subjects studied in the CHOICE study are shown in Table 1. The women were predominantly Caucasian (95%) and all variables were similar across all treatment arms.

Number and severity of hot flushes

Both ultra-low-dose treatments were effective in decreasing the number of moderate to severe hot flushes as well as their severity. The mean score of moderate to severe hot flushes showed a rapid response to treatment in both active groups. By week 3, the decrease in mean number of moderate to severe hot flushes for the ultra-low-dose treatment groups was statistically significant (all $p \leq 0.001$) when compared to the placebo group (see Figure 1). This rapid and significant reduction continued through week 12 and was then maintained until the conclusion of study.

In the ultra-low-dose 0.1 Group, the mean number of moderate to severe hot flushes dropped from 70.9 at baseline to 13.2 per week at week 12,

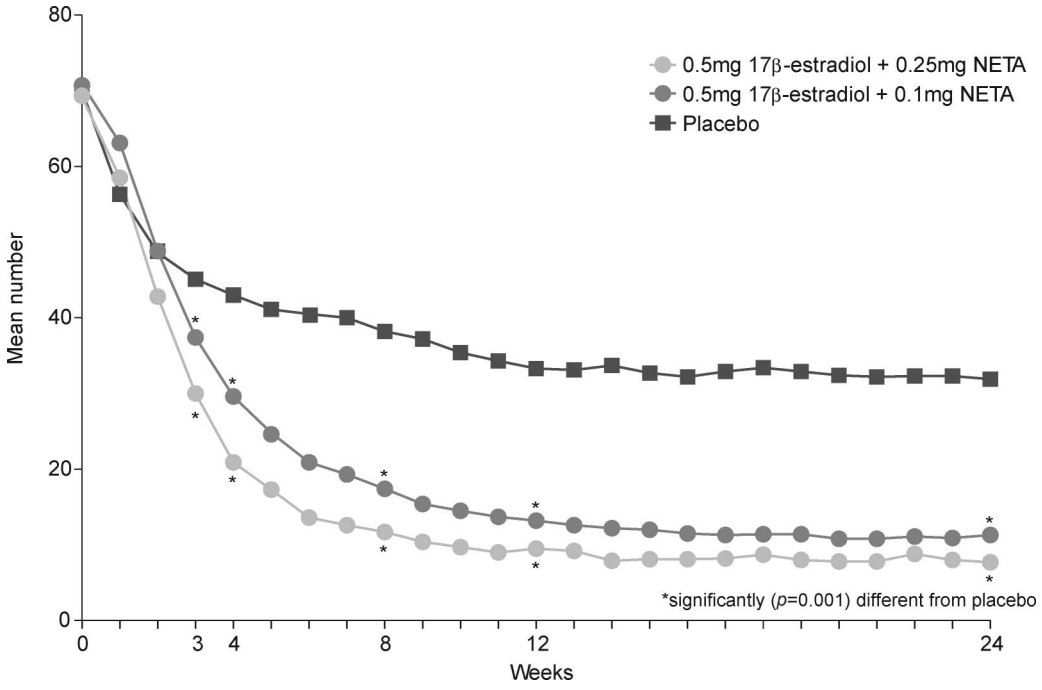

Figure 1 Number of moderate to severe hot flushes by week: intention-to-treat population. NETA, norethisterone acetate

while in the ultra-low-dose 0.25 Group, the mean number of moderate to severe hot flushes dropped from 69.2 at baseline to 9.5 per week at week 12. In the placebo group, the number of moderate to severe hot flushes fell during the trial but to a much lower degree, from 70.0 at baseline to 33.3 per week at week 12. There were no significant differences between the active treatment arms of the study. Figure 1 shows the decrease in mean number of moderate to severe hot flushes throughout the study.

Similarly to the number of hot flushes, the severity score for moderate to severe hot flushes also showed a statistically significant (all $p = 0.001$) decline by week 3 for both active treatment arms compared to placebo, with further improvement to week 12. The reduction at week 12 was maintained for the rest of the study. Overall, there were no differences between the active treatment arms (Table 3).

Subgroup analyses were carried out on the changes in the number and severity of moderate to severe hot flushes in subjects aged less than 50 years, 50–59 years and over 59 years. There were no notable differences between the age subgroups over the course of the trial. Additionally, no differences were noted in the severity score for hot flushes between the different age subgroups over the course of the trial.

HFWWS decreases

The HFWWS decrease (Figure 2) from baseline showed a statistically significant ($p \leq 0.001$) treatment difference that was seen at all assessed time points (4, 8, 12, and 24 weeks) compared to placebo, but no significant treatment differences were seen between the 0.1 and 0.25 Groups at any of the time points assessed. At week 12, decreases from baseline in mean HFWWS were from 185.8 to 35.8 in the 0.1 Group, from 180.5 to 26.6 in the 0.25 Group and a smaller decline from 183.5 to 89.7 for the placebo group.

Responder analysis

Responders were defined as subjects with at least a 90% improvement in HFWWS from baseline, as in a previous study[14]. A responder analysis also showed a statistically significant overall treatment effect at weeks 4, 8, 12 and 24 (all $p = 0.001$) for both active treatment groups. At week 12, the proportion of responders to the active treatments was 56% (95% confidence interval (CI) 49–63%), 67% (95% CI 60–74%) and 20% (95% CI 14–25%) for the 0.1 Group, 0.25 Group and placebo, respectively. At week 24, the proportion of responders was 66% (95% CI 59–73%) for the 0.1 Group, 75% (95% CI 69–81%) for the 0.25 Group and 23% (95% CI 17–28%) for the placebo group.

Greene Climacteric Scale scores

Both ultra-low-dose groups showed statistically significant decreases in Greene Climacteric Scale total score at all assessed time points when compared to the placebo group (all $p = 0.001$). Figure 3 summarizes the Greene Climacteric Scale data with total symptom scores for the ITT population. No differences were seen between the active treatment arms.

Difficulty in sleeping showed marked decreases in the active treatment groups over the course of the trial as well. There was a statistically significant (all $p \leq 0.001$) difference for both active groups compared to the placebo group at weeks 4, 8, 12 and 24. Participants that had no

Table 3 Subject disposition

	NETA 0.1	*NETA 0.25*	*Placebo*	*Total*
Number randomized	194 (100%)	182 (100%)	201 (1005)	577 (100%)
Received study medication	194 (100%)	181 (99%)	200 (100%)	575 (100%)
Withdrew	17 (9%)	10 (5%)	40 (20%)	67 (12%)
Reason for withdrawal				
Adverse event	11 (6%)	4 (2%)	16 (8%)	31 (5%)
Ineffective therapy	3 (2%)	2 (1%)	16 (8%)	21 (4%)
Non-compliance	3 (2%)	3 (2%)	2 (1%)	8 (1%)
Other reason	0	2 (1%)	7 (3%)	9 (2%)
Completed study	177 (91%)	171 (94%)	160 (80%)	508 (88%)

NETA, norethisterone acetate

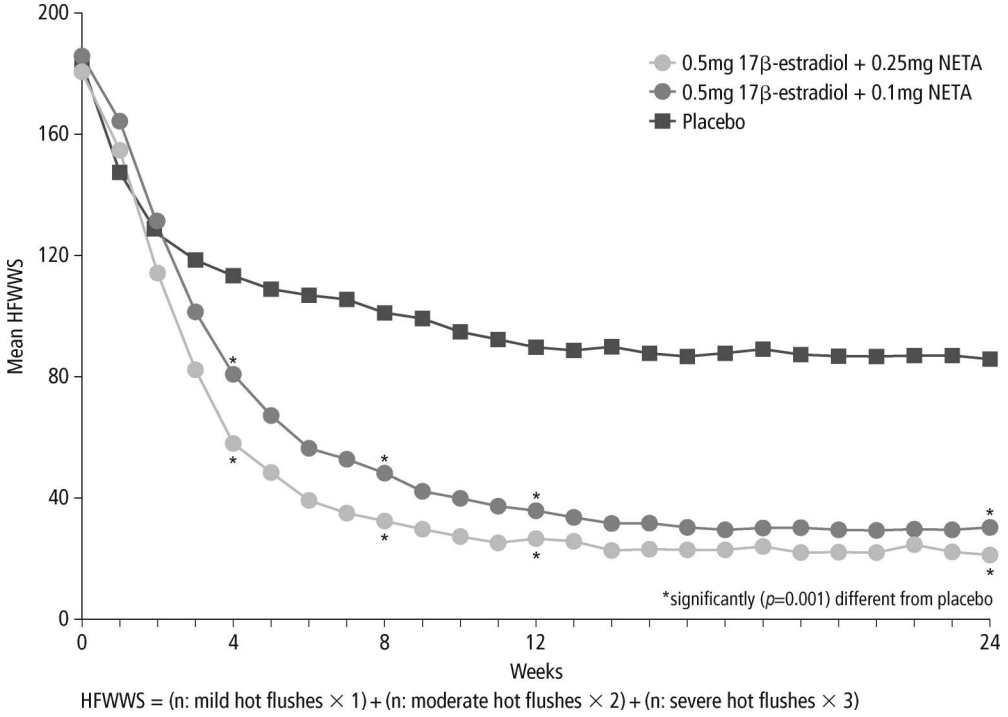

Figure 2 Hot flush weekly weighted score by week: intention-to-treat population. NETA, norethisterone acetate

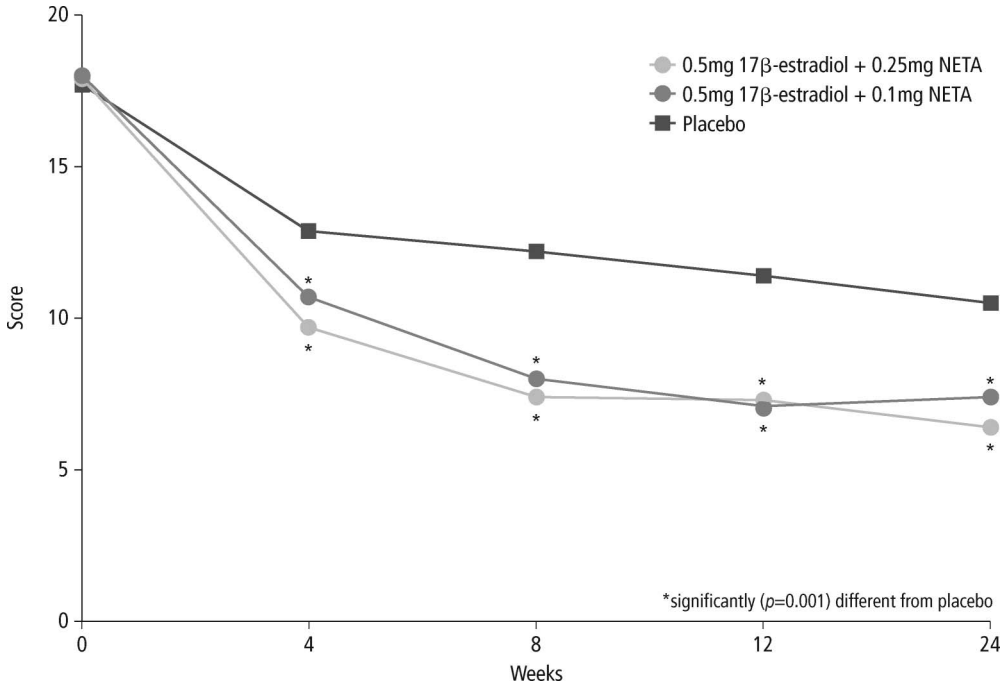

Figure 3 Greene Climacteric Scale: total symptoms score by week. NETA, norethisterone acetate

difficulty sleeping increased from 15% to 55% in the 0.1 Group, from 11% to 60% in the 0.25 Group, and from 19% to 35% for the placebo group by week 24. Women who had the greatest difficulty sleeping at baseline showed the best improvements across the three groups, but the magnitude of the improvement was smaller for those receiving placebo. There was no significant

difference in the positive scores between the two ultra-low-dose groups. Figure 4 summarizes the difficulty in sleeping changes in the respective active treatment arms.

Urogenital symptoms

Due to the relatively young average age of the trial population, urogenital symptoms associated with later-stage menopause were quite low at baseline. However, scores revealed a decrease in vaginal dryness in the ultra-low-dose groups compared to the placebo group. Maturation value and vaginal pH showed statistically significant ($p \leq 0.001$) changes in the treatment groups compared to the placebo at weeks 12 and 24 (Figure 5). No difference between the two ultra-low-dose groups was noted. The maturation value was calculated by multiplying the percentage of each cell type by the following factors: 0.2 for parabasal, 0.6 for intermediate and 1.0 for superficial cells.

ITT and PP population results

There were no notable differences in the results of the ITT and PP populations.

Safety results

The good tolerability and minimal side-effects of the two ultra-low-dose ccHRT preparations resulted in a very low drop-out rate for the two active groups. In the ultra-low-dose 0.1 Group, 91% ($n = 177$) of subjects completed the trial, while, for the ultra-low-dose 0.25 Group, the rate was 94% ($n = 171$). For the placebo group, 80% ($n = 160$) of the participants completed the trial. The major reason for higher withdrawal in the placebo group was ineffective therapy, 8% ($n = 16$); this reason was only reported in 2% ($n = 3$) and 1% ($n = 2$) in the ultra-low-dose 0.1 and 0.25 Groups, respectively. Figure 6 details the reasons for withdrawal across the three study populations and the final subject disposition. Most adverse events were classified as mild or moderate in severity, occurring only sporadically. Adverse events were cited as the reason for withdrawal in 6% ($n = 11$) of the ultra-low-dose 0.1 Group and 2% ($n = 4$) of the ultra-low-dose 0.25 Group, compared to 8% ($n = 16$) in the placebo group.

No changes in weight gain or blood pressure were reported over the course of the trial in the

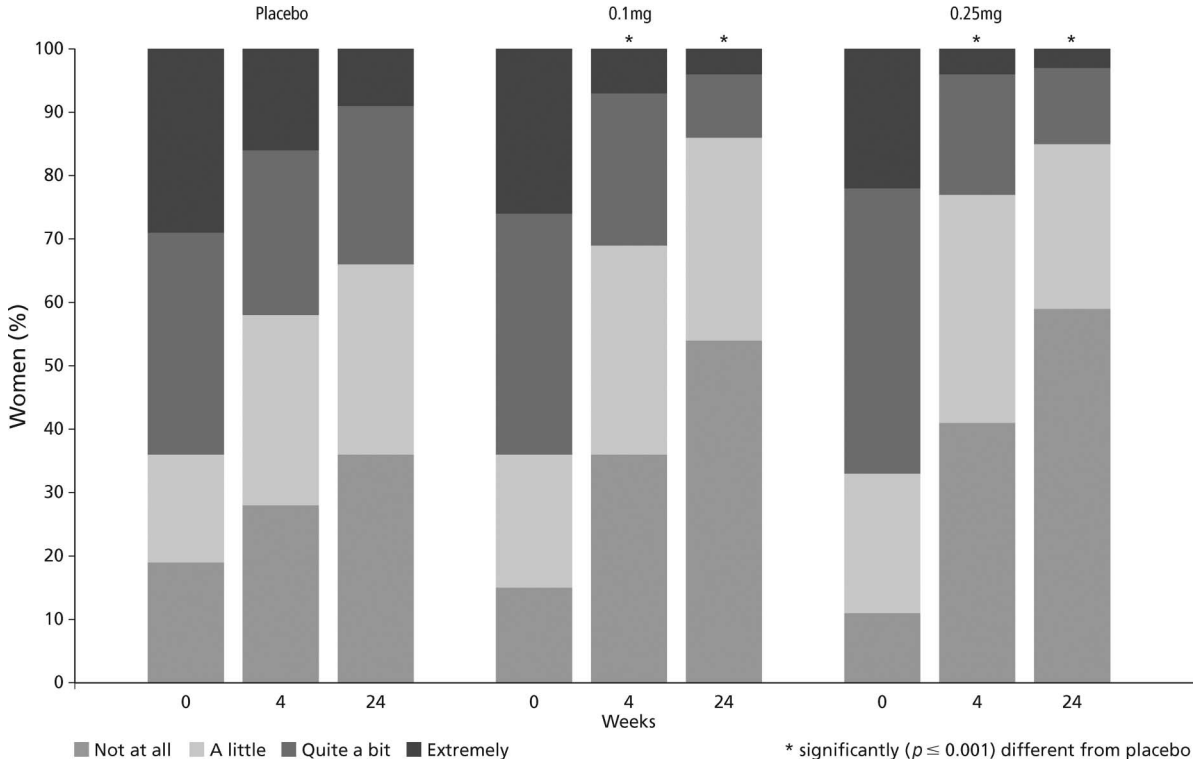

Figure 4 Difficulty in sleeping by week

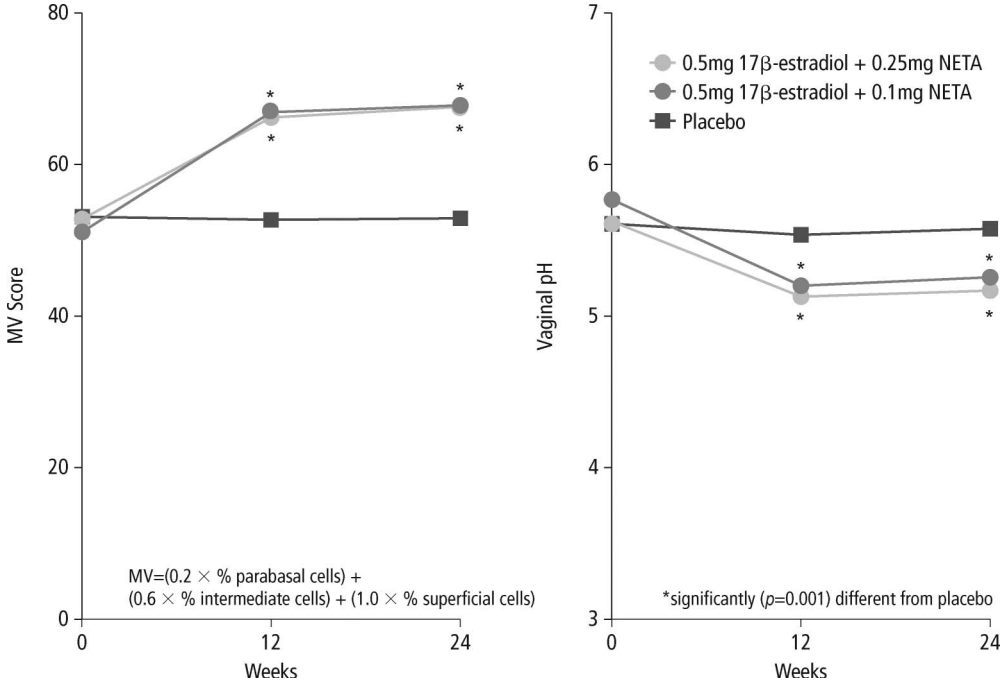

Figure 5 Maturation value (MV) and vaginal pH. NETA, norethisterone acetate

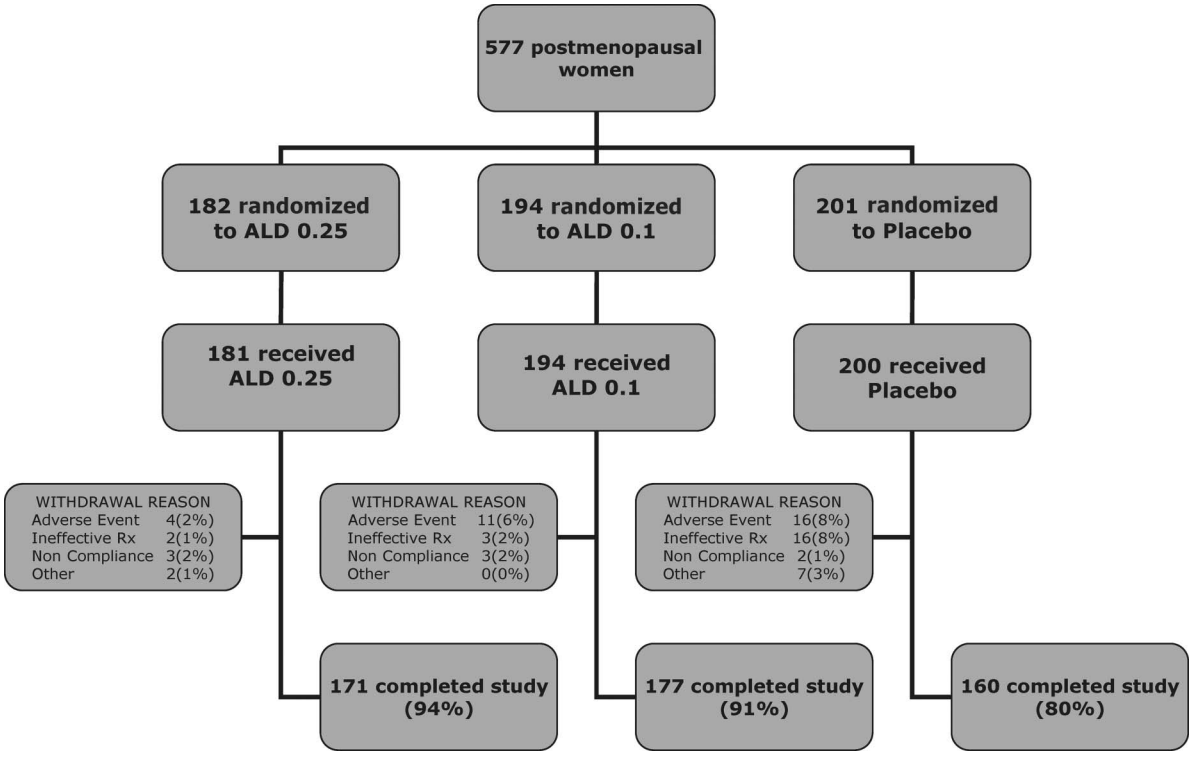

Figure 6 CONSORT flow chart for CHOICE trial. ALD 0.25, 0.5 mg 17β-estradiol + 0.25 mg norethisterone acetate; ALD 0.1, 0.5 mg 17β-estradiol + 0.1 mg norethisterone acetate

active groups. Breast pain, tenderness or discomfort were reported by only 3% ($n = 4$) and 2% ($n = 3$) in the 0.1 and 0.25 Groups, respectively. This was similar to the rate reported in the placebo group (3%, $n = 5$). Equally positive was the bleeding profile, with 89% of the ultra-low-dose groups

bleed-free by cycle 6. Both active treatment groups also had significant reductions in fibrinogen and Factor VII levels compared to the placebo group. These results, combined with the absence of thromboembolic events, suggest that detrimental cardiovascular events may not be a concern with the two ultra-low-dose formulations. Importantly, all safety parameters remained within normal limits for both the ultra-low-dose groups.

A detailed analysis of the bleeding pattern, endometrial safety and other safety data will be presented in separate publications.

DISCUSSION

The efficacy of ccHRT for the relief of climacteric symptoms in menopausal women is well established, making it the first-choice treatment, but recently there has been a call for more research into lower-dose options. Lowering the dose of HRT has been explored since the 1990s, with trials documenting the efficacy of 1 mg 17β-estradiol or 0.3 mg and 0.45 mg CEE and other formulations such as nasal estrogen[14,19–26]. Benefits with lower doses have been demonstrated not only for vasomotor symptoms but also for quality-of-life issues[27,28]. However, much of the focus has been upon lowering estrogen dosage, even though progestogens also play an important role[29,30].

A 12-week study by Notelovitz and colleagues[14], evaluating the efficacy of unopposed 17β-estradiol on moderate to severe vasomotor symptoms, compared doses ranging from 0.25 mg to 2.0 mg. By week 4, the 1 mg and 2 mg 17β-estradiol groups showed a statistically significant effect compared to placebo, while the 0.5 mg dose achieved statistical significance at week 8. The lowest investigated dose of 0.25 mg 17β-estradiol was not statistically different from placebo.

The CHOICE study results reflect similar positive results with ultra-low-dose ccHRT combinations of 0.5 mg 17β-estradiol + 0.1 mg NETA or 0.5 mg 17β-estradiol + 0.25 mg NETA in the reduction of moderate to severe hot flushes and number of responders, but with a more rapid effect. In CHOICE, statistical significance compared to placebo was reached by week 3 for all primary endpoints. Other investigated parameters also showed rapid, significant reduction in the active treatment groups compared to placebo, including the hot flush weekly weighted score.

The Greene Climacteric Scale scores, particularly 'difficulty in sleeping', also achieved rapid, statistically significant improvement. There were also significant improvements in vaginal maturation values and vaginal pH, even in this relatively young population who did not necessarily complain of urogenital symptoms at trial entry. Once again, improvements in these outcome measures with these ultra-low-dose combinations are comparable to the benefits previously achieved with higher-dose preparations.

The difference in reaching statistical significance of the ultra-low-dose treatment in the CHOICE trial (by week 3) compared to the Notelovitz study[14] (by week 8) can be explained by a larger sample size, but also can be attributed to the addition of NETA. The addition of low-dose NETA (0.5 mg) to 1 mg 17β-estradiol has been shown to enhance vasomotor symptom relief, compared to 1 mg of 17β-estradiol alone or placebo[29]. The positive additive effect of NETA on vasomotor symptom relief was seen as early as week 4 and has also been noted in previous studies[30].

Currently available estrogen efficacy data on vasomotor symptom relief indicate that there is a positive dose–response effect, i.e. a higher estrogen dose results in a greater reduction of symptoms. However, data also show that higher estrogen doses also result in a higher incidence of side-effects, including breast pain and bleeding, and in increased risks such as venous thromboembolism and stroke[7,8]. These side-effects and risks are significant concerns for both patients and prescribers. Reduction of unwanted side-effects and risks, while maintaining efficacy, should therefore result in improved continuation and uptake of therapy[3–6,31].

CONCLUSION

In response to the growing interest in finding the lowest effective dose of HRT, the CHOICE trial offers two new treatment options for effective relief of debilitating menopausal symptoms in climacteric women. The 0.5 mg 17β-estradiol + 0.1 mg NETA and 0.5 mg 17β-estradiol + 0.25 NETA preparations were both superior to placebo in efficacy, achieving statistically significant differences in hot flush occurrence and severity by week 3. This is comparable to the efficacy achieved with higher-dose preparations currently available on the market. Significant improvements were also reported in the secondary endpoints of HFWWS and the Greene Climacteric Scale. Benefits were sustained and improved over the course of the study. Overall, there was no statistically significant

difference in efficacy between the two active ultra-low-dose formulations.

In conjunction with previous study findings[14], the CHOICE data reveal that, currently, the lowest documented effective 17β-estradiol dose for menopausal symptom relief is 0.5 mg. Considering current concerns with the risk/benefit profile of HRT and the regulatory authority requirement to use the lowest effective dose, we suggest that the ultra-low-dose preparations of 0.5 mg 17β-estradiol + 0.1 mg NETA or 0.5 mg 17β-estradiol + 0.25 NETA should be considered as the new initial starting dose for the relief of menopausal symptoms in the majority of menopausal women.

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