

MENOPAUSE

Bleeding profile and endometrial safety of continuous combined regimens 1 mg 17 β -estradiol/trimegestone versus 1 or 2 mg 17 β -estradiol/norethisterone acetate in postmenopausal women

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Abstract

Objective. To compare the bleeding profile and endometrial safety of continuous combined 1 mg 17 β -estradiol (17 β -E₂) and 0.125 mg trimegestone (TMG) with those of two continuous combined 17 β -E₂ and norethisterone acetate (NETA) regimens.

Study design. This was a double-blind, randomized, multicenter study conducted in 12 European countries and Israel over a 2-year period. Healthy postmenopausal women with an intact uterus were given either 1 mg 17 β -E₂/0.125 mg TMG, 2 mg 17 β -E₂/1 mg NETA or 1 mg 17 β -E₂/0.5 mg NETA for up to 26 cycles, each of 28 days.

Results. The percentage of amenorrheic women was greater in most cycles up to cycle 13 in the 1 mg 17 β -E₂/0.125 mg TMG group than in the comparator groups. The mean number of bleeding days was similar in the 1 mg 17 β -E₂/0.125 mg TMG and the 1 mg 17 β -E₂/0.5 mg NETA groups, but greater in the 2 mg 17 β -E₂/1 mg NETA group. No endometrial hyperplasia was observed for any group.

Conclusion. Continuous combined 1 mg 17 β -E₂/0.125 mg TMG exhibits a more favorable bleeding profile than 1 mg 17 β -E₂/0.5 mg NETA up to 1 year, while providing an adequate protective effect on the endometrium.

Keywords: Trimegestone, estradiol, norethisterone acetate, continuous combined hormone replacement therapy, menopause, bleeding profile, endometrial safety, amenorrhea

Introduction

The decline in endogenous estrogen level at the time of menopause is associated with a wide range of symptoms, including hot flushes, night sweats, mood changes and sleep disturbances. Administration of unopposed estrogen significantly reduces these symptoms [1]; however, it is associated with an increased risk of endometrial hyperplasia and cancer [2,3]. Therefore, in women with an intact uterus, a combined treatment of estrogen and progestin is needed in order to protect the endometrium [4–7].

Trimegestone (TMG) is a novel 19-norpregnane derivative with a high relative binding affinity for the progesterone receptor and selectivity to the endometrium. Its pharmacologic profile has confirmed it is strongly progestogenic, but also very specific; it is devoid of androgenic, glucocorticoid, antigluco-corticoid, mineralocorticoid and estrogenic activity.

In preclinical studies it has been shown to possess some antiandrogenic and antiminerlocorticoid activity, but only at doses higher than those used in human subjects [8]. Moreover, in studies analyzing its potential interaction with the γ -aminobutyric acid receptor system [9], it seems to have a minimal impact on this system, suggesting it may have less impact on mood than other progestogens [10,11]. Thus, a hormone therapy that combines 17 β -estradiol (17 β -E₂) with TMG should prevent endometrial hyperplasia and cause minimal interference with the desired effects of estradiol.

The use of TMG in combination with 17 β -E₂ has been investigated in a number of clinical studies [12–19]. Treatment with continuous combined 2 mg 17 β -E₂/0.5 mg TMG has been shown to have a protective effect on the endometrium and to provide a good bleeding profile [16]. Continuous combined estrogen/progestogen treatments have been reported

to minimize endometrial proliferation, leading mainly to atrophy, and to minimize uterine bleeding, leading to amenorrhea in most women [20,21]. In addition, lowering the dose of estradiol can improve the bleeding profile, increase the rate of amenorrhea and reduce estrogen-associated adverse events. Therefore, a continuous combined regimen of 1 mg 17 β -E₂/0.125 mg TMG may offer clinical advantages to women who desire lower doses of estradiol to treat menopausal symptoms using a regimen without a withdrawal bleeding period.

The main objectives of the present study were to compare 17 β -E₂/0.125 mg TMG and two 17 β -E₂/norethisterone acetate (NETA) preparations in terms of efficacy in relieving postmenopausal symptoms, and safety in preventing endometrial hyperplasia. This paper reports the endometrial bleeding and safety profiles, with the efficacy findings reported elsewhere [22].

Methods

Study design and population

This was a double-blind, randomized, multicenter study. Details of the study design, study population and clinical examination are reported in the accompanying paper [22].

Bleeding profile

A daily menstrual diary card was completed by all women, who recorded bleeding data as: 0, none; 1, spotting (requiring no sanitary protection); 2, light bleeding; 3, moderate bleeding; or 4, heavy bleeding. The bleeding profile included a classification of women who were amenorrheic and who had spotting/bleeding, as well as the duration and intensity of spotting and/or bleeding episodes.

Endometrial histology

An endometrial biopsy was performed at screening and at cycles 13 and 26 for women enrolled in the comparative study. Samples were collected using a Pipelle endometrial sampling device or a Vabra suction curette. If the histological result for the last endometrial biopsy assessment was 'no endometrium identified' or 'endometrial tissue insufficient for diagnosis', transvaginal ultrasonography performed during treatment was used to confirm the endometrial atrophy [23,24]. The above-mentioned histological categories were then re-categorized as 'endometrium tissue - other' (i.e., atrophic or inactive endometrium). If the atrophy was not confirmed by ultrasound, no re-categorization was performed. Biopsies were assessed by two independent pathologists blinded to study treatment. In the case of disagreement between the two pathologists on a diagnosis of hyperplasia or carcinoma, a third

pathologist reviewed the slides and the final decision was based on the diagnosis of the majority.

Safety

Adverse events observed by the investigator or reported by a woman spontaneously were documented and assessed by the investigator in terms of severity and relationship to treatment. Concomitant medications were also documented. Treatment compliance was evaluated by a capsule or tablet count at each cycle.

Statistical analyses

All women randomly assigned to treatment were included in the safety population irrespective of study drug intake. Treatment groups were statistically compared at baseline to assess the effectiveness of randomization. Continuous variables were compared using one-way analysis of variance (ANOVA) with treatment as a factor. Categorical variables were compared with the χ^2 test.

Analysis of the bleeding profile parameters was conducted on the intent-to-treat (ITT) population (primary population), defined as all randomized women who had at least 1 day's assessment of the primary efficacy variable during the 7-day screening phase and during the on-therapy phase, and had taken at least one dose (or partial dose) of the study drug. At each cycle, a logistic regression with treatment and center grouping as factors was used to study the percentage of amenorrheic women. A two-way ANOVA with the same factors was used to analyze the number of bleeding/spotting days.

For the primary safety assessment, endometrial hyperplasia, it has been hypothesized that the incidence rate could vary between 1% and 2% after 1 to 2 years. With 300 women in the 1 mg 17 β -E₂/0.125 mg TMG (i.e., after 1 year), the upper 95% confidence limit was to be approximately 2.13%, 2.80% or 3.58% if the incidence rate was 1%, 1.5% or 2%, respectively. Fisher's exact test was used to test for a difference between treatment groups for non-serious adverse events when the incidence was $\geq 10\%$ in at least one of the treatment groups. Efficacy and safety tests were two-sided with the significance level set at 5%.

Results

The demographic characteristics, including menopausal history, for the three treatment groups are shown in Table I. Overall differences were detected for the time since last menstrual period and current tobacco usage in the safety population. In addition, differences in weight, body mass index (BMI) and current tobacco usage were also detected between women enrolled in the 1 mg 17 β -E₂/0.125 mg TMG groups in Part 1 and those enrolled in Part 2. These

Table I. Baseline demographic characteristics of the safety population.

Variable	1 mg 17 β -E ₂ /0.125 mg TMG (n = 462)	2 mg 17 β -E ₂ /1 mg NETA (n = 200)	1 mg 17 β -E ₂ /0.5 mg NETA (n = 249)
Age (years)	53.0	54.0	53.0
Ethnic origin (n)			
White	459	200	248
Black	1		1
Other	2		
Height (cm)	163.2 \pm 6.7	163.7 \pm 6.3	163.1 \pm 5.9
Weight (kg)	67.2 \pm 10.2	66.2 \pm 9.6	67.3 \pm 9.9
Body mass index (kg/m ²)	25.2 \pm 3.4	24.7 \pm 3.1	25.3 \pm 3.7
Years since last natural menstrual period	4.8 \pm 4.4	5.1 \pm 4.1	4.1 \pm 3.6
Smoking status (n)			
Smoker	108	36	71
Non-smoker	354	164	178
Current tobacco usage (cigarettes per day)	2.3 \pm 4.5	1.8 \pm 4.1	3.0 \pm 5.2
Current alcohol usage (n)			
< 720 ml beer/day	456	195	244
> 720 ml beer/day	2	2	4

17 β -E₂, 17 β -estradiol; TMG, trimegestone; NETA, norethisterone acetate; data are expressed as mean \pm standard deviation (or n, when indicated).

parameters, especially tobacco usage, have been shown to potentially interfere with several effects of HRT [25,26]. Therefore, two series of additional analyses were performed including BMI, number of cigarettes smoked per day and time since last menstrual period as covariates.

Adverse events were a reason for discontinuation of treatment for 16%, 28% and 15% of women in the 1 mg 17 β -E₂/0.125 mg TMG, 2 mg 17 β -E₂/1 mg NETA and 1 mg 17 β -E₂/0.5 mg NETA groups, respectively. Compliance was assessed by counting the number of active tablets or capsules the women missed at each cycle, as reported in the diary cards. At cycle 12, at least 98% of the women were at least 90% compliant in the 1 mg 17 β -E₂/0.125 mg TMG and 1 mg 17 β -E₂/0.5 mg NETA groups. At cycle 25, compliance was greater than 95% in the 1 mg 17 β -E₂/0.125 mg TMG and 2 mg 17 β -E₂/1 mg NETA groups.

Bleeding profile

The percentage of women with amenorrhea in a given cycle increased steadily throughout the study in the three treatment groups, with the highest percentage observed in the group receiving 1 mg 17 β -E₂/0.125 mg TMG (Figure 1).

The percentage of amenorrheic women was greater in most cycles up to cycle 13 in the 1 mg 17 β -E₂/0.125 mg TMG group than in the comparator groups, using the logistic regression with tobacco usage, time since last menstrual period and BMI as covariates (with a significant difference at cycles 4, 5, 6, 7, 8 and 9 vs. the 2 mg 17 β -E₂/1 mg NETA comparator and at cycles 8, 10, 11 and 12 vs. the 1 mg 17 β -E₂/0.5 mg NETA comparator). At cycle 12, the percentage of women with amenorrhea was

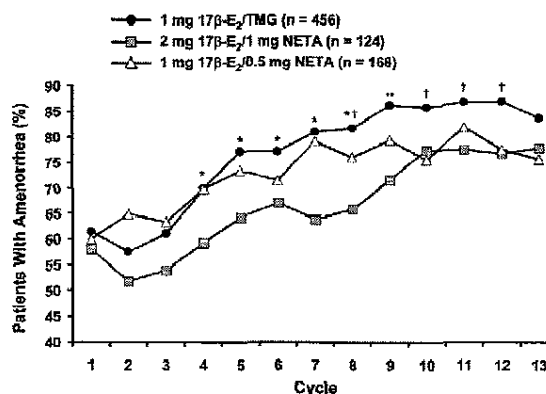


Figure 1. Percentage of women with amenorrhea by cycle in three treatment groups: 1 mg 17 β -estradiol (17 β -E₂)/0.125 mg trimegestone (TMG), 2 mg 17 β -E₂/1 mg norethisterone acetate (NETA) and 1 mg 17 β -E₂/0.5 mg NETA. * p < 0.01, ** p < 0.001, 1 mg 17 β -E₂/0.125 mg TMG versus 2 mg 17 β -E₂/1 mg NETA; † p < 0.01, 1 mg 17 β -E₂/0.125 mg TMG versus 1 mg 17 β -E₂/0.5 mg NETA.

87% in the 1 mg 17 β -E₂/0.125 mg TMG group, compared with 76% in the 2 mg 17 β -E₂/1 mg NETA group (p = 0.04) and 78% the 1 mg 17 β -E₂/0.5 mg NETA group (p = 0.01).

The mean number of bleeding/spotting days at cycle 13 was similar in the 1 mg 17 β -E₂/0.125 mg TMG and 1 mg 17 β -E₂/0.5 mg NETA groups (6.5 and 6.48, respectively) and larger in the 2 mg 17 β -E₂/1 mg group (8.56), as expected due to its higher estrogen dose (Figure 2). The mean severity of bleeding/spotting episodes for 1 mg 17 β -E₂/0.125 mg TMG was lower than for the two other treatments in all cycles except cycles 1 and 2, but no statistical comparisons were performed. The number

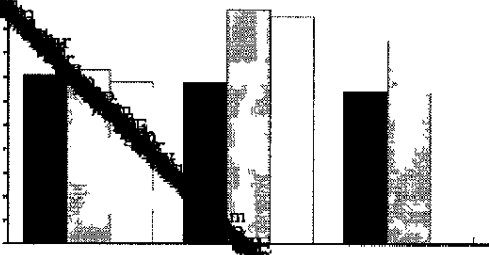
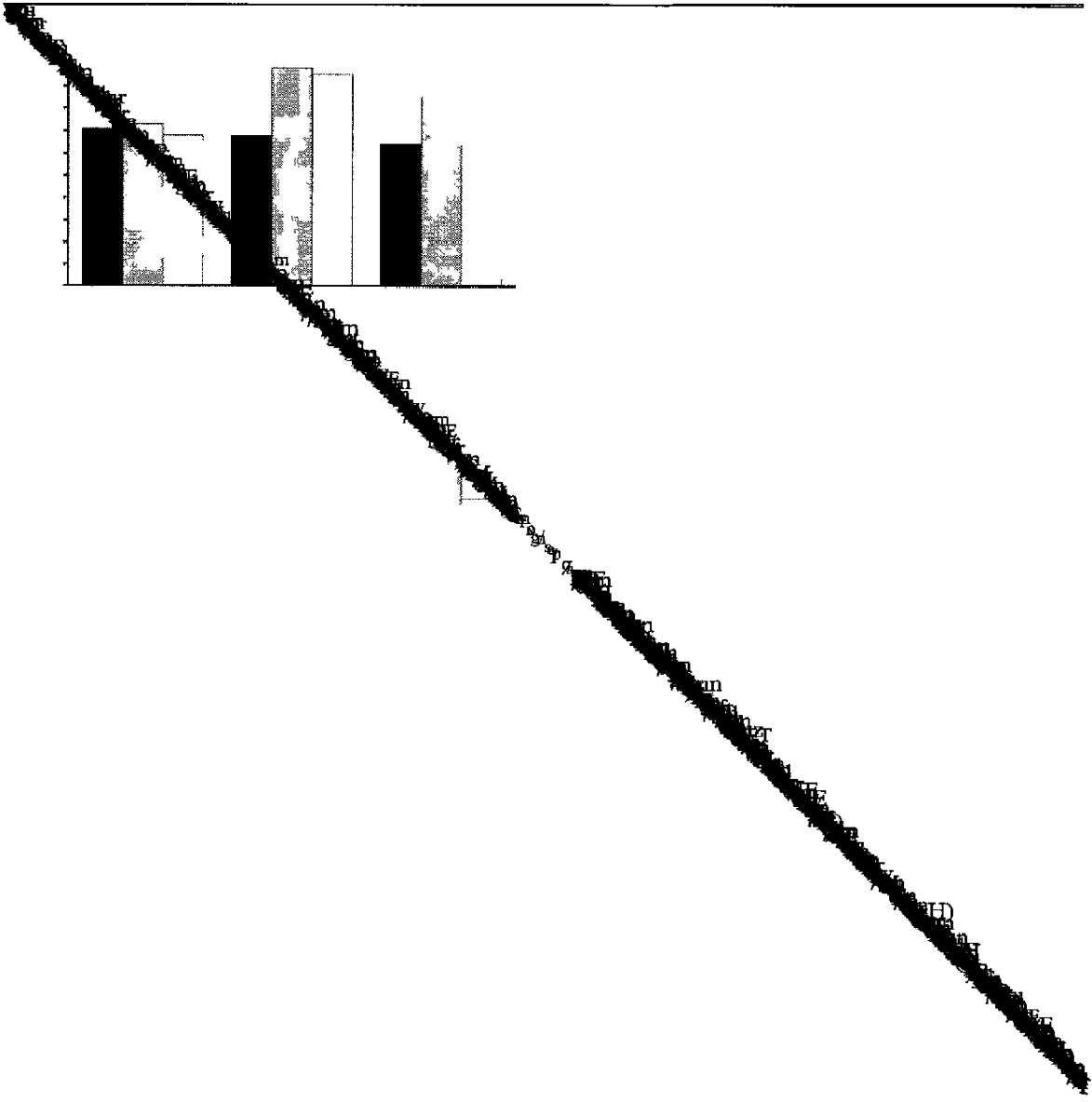


Table III. Endometrial patterns in women treated for 1 or 2 years with three continuous regimens.

	1-year regimen				2-year regimen			
	1 mg 17 β -E ₂ /0.125 mg TMG		1 mg 17 β -E ₂ /0.5 mg NETA		1 mg 17 β -E ₂ /0.125 mg TMG		2 mg 17 β -E ₂ /1 mg NETA	
	Screening	≥ Cycle 12	Screening	≥ Cycle 12	Screening	≥ Cycle 25	Screening	≥ Cycle 25
Evaluative biopsies	204 (84)	168 (87)	208 (84)	160 (84)	177 (83)	108 (84)	161 (83)	86 (83)
Atrophic, inactive	182 (75)	142 (74)	179 (72)	130 (68)	150 (70)	97 (76)	134 (69)	69 (57)
Secretory	0	1 (1)	4 (2)	3 (2)	2 (1)	1 (1)	1 (1)	3 (3)
Progesterin effect	0	10 (5)	1 (0)	8 (4)	0	4 (3)	1 (1)	4 (4)
Menstrual	1 (0)	1 (1)	2 (1)	4 (2)	2 (1)	0	2 (1)	2 (2)
Benign endometrial polyp	3 (1)	9 (5)	2 (1)	6 (3)	3 (1)	2 (2)	1 (1)	3 (3)
Proliferative	18 (7)	5 (3)	20 (8)	9 (5)	20 (9)	4 (3)	22 (11)	5 (5)
Hyperplasia	0	0	0	0	0	0	0	0
Carcinoma	0	0	0	0	0	0	0	0

17 β -E₂, 17 β -estradiol; TMG, trimegestone; NETA, norethisterone acetate; data are expressed as n (%).

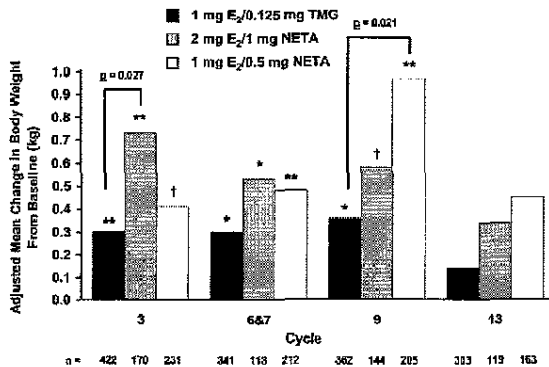


Figure 3. Mean body weight changes observed up to cycle 13, in women treated with 1 mg 17 β -estradiol (17 β -E₂) and either 0.125 mg trimegestone (TMG) or 0.5 mg norethisterone acetate (NETA). Pairwise comparison between groups using analysis of covariance (covariates: weight at baseline, body mass index at baseline, ranked number of cigarettes, log [years]). * $p < 0.05$, ** $p < 0.01$, † $p < 0.001$, versus baseline.

available for a proportion of the study population who met this criterion in Part 2 of the study. Estradiol levels in the groups receiving either 1 mg 17 β -E₂/0.125 mg TMG or 1 mg 17 β -E₂/0.5 mg NETA showed that, although there was the same exogenous intake of 17 β -E₂ in both, mean estradiol levels at cycles 7 and 13 were higher in the latter than in the former group (Table IV). These results are indicative of a possibly higher endogenous estradiol secretion with 1 mg 17 β -E₂/0.5 mg NETA.

Two possible clinical consequences arising from excess endogenous secretion of estradiol were evaluated: bleeding and/or spotting, and breast pain. The percentages of women with bleeding and/or spotting between cycle 1 and 3 were similar in the 17 β -E₂/0.125 mg TMG and 1 mg 17 β -E₂/0.5 mg NETA groups (40.3% and 38.8%, respectively). But during cycles 6–8, the corresponding percentages were 11.6% and 21.9%, and for cycles 11–13, 9.3% and 16.5%, showing a trend to a better bleeding

Table IV. Mean change from baseline of serum levels of estradiol 6–12 months after menopause.

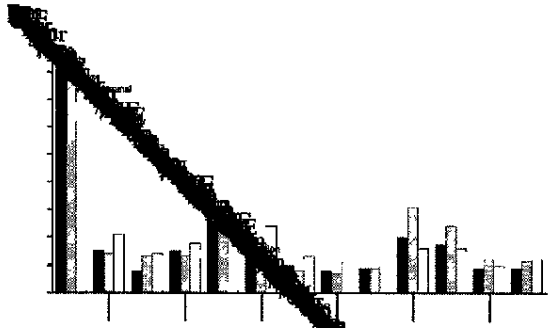
	Estradiol (pg/ml)	
	1 mg 17 β -E ₂ /0.125 mg TMG	1 mg 17 β -E ₂ /0.5 mg NETA
Cycle 7	65.0 ± 15.0** (25)	122.6 ± 42.7* (25)
Cycle 13	28.5 ± 4.7** (22)	42.2 ± 4.9** (16)

17 β -E₂, 17 β -estradiol; TMG, trimegestone; NETA, norethisterone acetate; data are expressed as mean ± standard error of the mean (n); statistically significant difference from baseline: * $p < 0.01$, ** $p < 0.001$.

profile for 1 mg 17 β -E₂/0.125 mg TMG in these perimenopausal women. For breast pain, the percentages of women enrolled between 6 and 12 months following menopause were 15% and 18% for the 17 β -E₂/0.125 mg TMG and 1 mg 17 β -E₂/0.5 mg NETA groups, respectively. For the 17 β -E₂/0.125 mg TMG group, the percentage was not greater than for the whole study population (17% and 16% for 1 mg 17 β -E₂/0.125 mg TMG and 1 mg 17 β -E₂/0.5 mg NETA, respectively). These data on a limited number of women need to be confirmed in a larger population, but do provide confidence for prescribing the 1 mg 17 β -E₂/0.125 mg TMG continuous combination in the early period following the menopause, with adequate clinical follow-up.

Safety evaluation

All treatments were well tolerated and the percentages of women who experienced an adverse event were similar across the three groups. A total of 13 women experienced serious adverse events considered as possibly related to the study drug treatment. Of these, five women had been treated for less than 1 year (two women in the 1 mg 17 β -E₂/0.125 mg



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