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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.



V. Joseph

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Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:

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COMPOUNDS AND THEIR USES FOR ALLEVIATING MENOPAUSE-ASSOCIATED SYMPTOMS

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COMPOUNDS AND THEIR USES FOR ALLEVIATING MENOPAUSE-ASSOCIATED SYMPTOMS

Field of the invention

5 The present invention relates to hormone replacement therapy for alleviating menopause-associated symptoms which is based on the administration to a female mammal of an estetrol component at specified daily doses, optionally in combination with a progestogenic component.

 As further detailed herein, the therapy displays statistically significant efficacy combined with a favourable profile for side effects compared to currently available methods for alleviating
10 menopause-associated symptoms.

Background art

 Hormone replacement therapy (HRT) is used to describe either unopposed oestrogen use (for women who have undergone hysterectomy) or combined oestrogen-progestin therapy (for
15 women still having a uterus). The goal of HRT is to relieve menopausal symptoms, most importantly vasomotor symptoms (VMS), such as hot flushes. Other diseases and symptoms associated with perimenopause and menopause that respond to oestrogen therapy include osteoporosis, vaginal atrophy, and sleep disturbances (when related to hot flushes).

 VMS occur most often in the late menopausal transition and early post-menopause. VMS
20 are the most significant menopausal complaints. Estimates suggest that about 75% of women who are more than 50 years old will suffer from hot flushes (Utian et al., 2005, "*Comparative controlled trial of a novel oral estrogen therapy, estradiol acetate, for relief of menopause symptoms*" Menopause 12(6): 708-715). Most experience hot flushes for about two years, although around 10% suffer for more than 10 years (Rodstrom et al., 2002, "*A longitudinal study of the treatment of*
25 *hot flushes: the population study of women in Gothenburg during a quarter of a century*" Menopause 9(3): 156-161). VMS can contribute towards physical and psycho-social impairment, with a consequent reduction in quality of life, and are one of the main reasons why women may seek medical care for the menopause (Santoro, 2008, "*Symptoms of menopause: hot flushes*" Clin Obstet Gynecol 51(3): 539-548).

 The epithelial linings of the vagina and urethra are very sensitive to oestrogen, and
30 oestrogen deficiency leads to thinning both epithelia. This results in vulvovaginal atrophy (VVA) and urinary complaints, causing symptoms of vaginal dryness, itching, dyspareunia, dysuria, urinary frequency and an increased risk of recurrent urinary infections. In early 2014, the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause
35 Society (NAMS) endorsed the new terminology "genitourinary syndrome of menopause (GSM)" to replace the VVA terminology. The rationale for using this new terminology was that VVA term was too restrictive whereas GSM was a more comprehensive term that includes symptomatic VVA as well as lower urinary tract symptoms related to low oestrogen levels (Portman et al., 2014, "*Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the*

International Society for the Study of Women's Sexual Health and the North American Menopause Society" Menopause 21(10): 1063-1068) . Note that the GSM terminology has not yet been adopted in guidance for industry issued by the FDA and EMA, therefore the VVA terminology will be used herein.

5 Oestrogen therapy remains the gold standard for relief of menopausal symptoms, in particular hot flushes. All routes of administration appear to be equally effective for symptom relief, but their metabolic effects differ. Oestrogens should be administered continuously; past regimens where oestrogen was administered day 1 to day 25 of the calendar month are considered to be obsolete. Women will often get hot flushes during the days off, and there is no known advantage to
10 stopping for several days each month.

With current HRT, all women with an intact uterus need a progestin in addition to oestrogen to prevent endometrial hyperplasia – and subsequent carcinoma – which occurs after as little as 6 months of oestrogen therapy. The progestin may be administered continuously or sequentially (10 to 14 days each month or for 14 days every 3 months).

15 Oestrogen therapy is the most consistently effective treatment used in the US and Europe for menopausal VMS. Following the safety issues reported in the primary Women's Health Initiative publications (Anderson et al., 2004, "*Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial*" JAMA
20 291(14): 1701-1712) and with continued subject requests for treatment, a challenge to clinicians has been to identify the lowest effective dose of oestrogen for alleviating menopausal symptoms (Simon et al., 2007, "*Menopausal hormone therapy for vasomotor symptoms: balancing the risks and benefits with ultra-low doses of estrogen*" Expert Opin Investig Drugs 16(12): 2005-2020). In addition, it is a challenge to develop a safer oestrogen than those currently used.

25 In a 2016 publication, Coelingh Bennink et al; ("*Clinical effects of the fetal estrogen estetrol in a multiple-rising-dose study in postmenopausal women*", Maturitas, 2016 Sep; 91:93-100) report a partly randomized, open-label, multiple-rising-dose study in 49 postmenopausal women who received either 2 mg estetrol or 2 mg estradiol-valerate per day for 28 days (randomized part of the
30 study) followed by dose-escalation at 10, 20 and 40 mg estetrol per day (non-randomized part of the study). The authors report a decrease in the mean number of hot flushes and sweating already with the 2 mg estetrol per day dose, while at the same time endometrial thickness was found to be stable in the 2 mg estetrol group but increasing in the 10 mg estetrol group (abstract).

35 From this study, the skilled person would learn that a daily dose of 2 mg estetrol is as effective as a daily dose of 10 mg estetrol at decreasing the number of hot flushes per day (see for example Figure 3 in Coelingh Bennink et al., Maturitas, 2016) and that the 2 mg daily dose does not alter endometrial thickness while the 10 mg daily dose has an important effect on endometrial thickness (see for example Figure 2 in Coelingh Bennink et al., 2016). The skilled person would
40 thus conclude that the Minimal Effective Dose of estetrol for the treatment of VMS is 2 mg per day.

Summary of the invention

Against this background, the present inventors have now surprisingly found that the Minimal Effective Dose of estetrol for the alleviation of VMS in postmenopausal women is of about 15 mg daily.

The determination of the Minimal Effective Dose indeed revolves around a number of parameters which take into account not only the mean number of hot flushes per day (as was done by Coelingh Bennink et al in Maturitas, 2016), but also the severity of hot flushes, and also a weekly weighted score, as further defined herein.

Thus, in terms of efficacy, it was surprisingly found that a daily dose of 15 mg was required to obtain a definite effect on VMS.

Furthermore, it was observed by the present inventors that several side effects of the treatment, as reflected for example in the number of treatment-emergent adverse events (TEAEs), or in the number of patients leaving the study in each group, or in the number of biopsies which had to be performed in each group, tend to reach a plateau at around 10 mg per day, and do not worsen when the dose is further increased. Surprisingly, some of these parameters in fact regress from 10 mg to 15 mg daily, thus indicating that the adverse events could be more bearable when the dose is higher than 10 mg per day.

Based on this surprising finding, and on measurements performed when a 20 mg daily dose is administered, the present inventors have thus come to the unexpected conclusion that an optimal daily dose of estetrol for alleviation of VMS in postmenopausal women is found in the range of 15 mg to 25 mg. This range of doses indeed allows statistically significant effects on VMS to be observed, as is shown in the examples, while maintaining the treatment side effects within an acceptable window.

Detailed description of the invention

Definitions

The term "estetrol component", as used throughout this document, encompasses substances selected from the group consisting of estetrol, esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; and combinations thereof. Even more preferably, the estetrol component is estetrol (including estetrol hydrates). Most preferably, the estetrol component contained in the dosage unit is estetrol monohydrate.

The term "estetrol" as used herein refers to 1,3,5 (10)-estratrien-3,15alpha,16alpha,17beta-tetrol or 15alpha-hydroxyestriol as well as hydrates of estetrol, e.g. estetrol monohydrate.

The term "progestogenic component" is defined as a substance that is capable of triggering a progestogenic response in vivo or a precursor which is capable of liberating such a substance in vivo. Usually progestogenic components are capable of binding to a progestogen receptor.

In the context of the present invention, other compounds may be used in conjunction with the estetrol component for administering to women who have a uterus. Selective Estrogen Receptor Modulators (SERMs) defines a category of such compounds, which are contemplated as useful complements to the estetrol component in the methods of the invention. A preferred SERM for use in the context of the present invention is bazedoxifene.

In the methods and compositions further described herein, it has to be understood that when reference is made to a "progestogenic component", such reference includes SERMs and in particular bazedoxifene.

"About" as used herein referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, is meant to encompass variations of +/-10% or less, more preferably +/-5% or less, even more preferably +/-1% or less of and from the specified value, in so far such variations are appropriate to perform in the disclosed invention. However, it is to be understood that the value to which the modifier "about" refers is itself also specifically disclosed.

The term "an effective amount" refers to an amount necessary to obtain a physiological effect. The physiological effect may be achieved by one dose or by repeated doses.

The terms "Hot Flush Weekly Weighted Score", as used herein, is calculated by adding:

- the number of mild hot flushes during 7 days multiplied by 1;
- the number of moderate hot flushes during 7 days multiplied by 2;
- the number of severe hot flushes during 7 days multiplied by 3; and

dividing the result by the total number of hot flushes during the 7 days.

Such a weighted score was for example used by Notelovitz et al. ("*Initial 17 β -Estradiol Dose for Treating Vasomotor Symptoms*"; Obstetrics and Gynaecology, Vol. 95(5), May 2000, p. 726-731).

Determination of the Minimum Effective Dose

To determine the Minimum Effective Dose (MED), firstly the selection criteria required that patients presented at least 7 moderate to severe hot flushes/day or at least 50 moderate to severe hot flushes/week in the week preceding randomization. Secondly, a placebo group was included in a double-blind fashion. Thirdly, the total patient number was such that statistical significance could be obtained between separate arms of the study. Finally, the absolute change from baseline in weekly frequency of moderate to severe VMS was taken into account. An analysis of covariance (ANCOVA) was performed based on the untransformed change in weekly frequency of moderate to severe VMS from baseline.

Hormone replacement therapy

The present therapy usually employs continuous administration of the estetrol component during a period of at least 10 days, preferably of at least 20 days.

5

The estetrol component is administered at a daily dose of from about 15 mg to about 25 mg.

In a specific embodiment, the estetrol component is administered at a daily dose of from about 15 mg to less than 20 mg.

In another specific embodiment, the estetrol component is administered at a daily dose of more than 20 mg to about 25 mg.

10

In one embodiment, the present therapy is administered to non-hysterectomized patients. In a particular embodiment, the present therapy involves daily administration of about 20 mg of the estetrol component, preferably to non-hysterectomized patients.

15

In the cases when the present therapy is administered to a patient who has undergone hysterectomy, the estetrol component is preferably administered as sole active ingredient.

When the present therapy is administered to non-hysterectomized patients, the optional progestogenic component may be administered continuously or sequentially (for example, 10 to 14 days each month or for 14 days every 3 months).

20

The terms "continuous" / "continuously" as used in here, means that the components are administered at relatively regular intervals, with no (therapeutically) significant interruptions. Naturally, minor interruptions may occur that do not affect the overall effectiveness of the present method, and indeed such aberrations are encompassed by the present invention. In a preferred embodiment, and more arithmetically, the administration regimen is deemed to be continuous if the longest interval between 2 subsequent administrations is not more than 3.5 times as long as the average interval. Even more preferably said longest interval is not more than 2.5 times, most preferably not more than 1.5 times as long as the average interval.

25

In one embodiment, the optional progestogenic component is administered via a non-oral route, for example using an Intra Uterine Device (IUD). In one embodiment said IUD delivers the progestogenic component levonorgestrel. In one such embodiment, the IUD is the Mirena® IUD or the Levosert® IUD.

30

In one embodiment, the present therapy employs oral, sublingual, buccal, or sublabial administration of the estetrol component. These modes of administration offer the advantages that the estetrol component does not have to pass through the digestive system and avoids first-pass liver exposure. Furthermore, these modes of administration provide a rapid onset of action.

35

The term "sublingual" as used herein refers to the pharmacological route of administration by which the estetrol component diffuses into the blood through tissues under the tongue.

The term "buccal" as used herein refers to the pharmacological route of administration by which the estetrol component diffuses into the blood through tissues of the buccal vestibule, the area inside the mouth between the lining of cheek (the buccal mucosa) and the teeth / gums.

5 The term "sublabial" as used herein refers to the pharmacological route of administration by which the estetrol component is placed between the lip and the gingiva.

In the present method, the estetrol and progestogenic components may be administered in separate dosage units. However, it is also possible and indeed very convenient to combine these two components into a single dosage unit.

10 In the method according to the present invention the combination of the progestogenic and estetrol component is suitably administered continuously during a period of at least 10 days.

The invention may suitably be reduced to practice in the form of a variety of administration methods that are known to the person skilled in the art. Amongst these methods are the methods making use of monophasic preparations, which contain dosage units with a constant amount of the
15 estetrol component and of the optional progestogenic component.

In the embodiment of the invention where sequential administration of the progestogenic component is chosen, it is also possible and convenient to combine the components into a single dosage unit for the days when the two components are administered.

20

Compositions

The estetrol component of the present invention encompasses substances selected from the group consisting of estetrol, esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid
25 or sulfamic acid of 1-25 carbon atoms; and combinations thereof. More preferably, the estetrol component is estetrol (including estetrol hydrates). Most preferably, the estetrol component contained in the dosage unit is estetrol monohydrate.

The estetrol component of the invention is used at a daily dose equivalent to from about 15 mg to about 25 mg of estetrol. In other words, when the estetrol component is not estetrol itself,
30 the daily dose of the estetrol component is adjusted to yield a therapeutic effect equivalent to that of a daily dose of about 15 mg to about 25 mg of estetrol.

In a particularly preferred embodiment of the invention the pharmaceutical composition according to invention is designed for daily administration, i.e. it represents a daily dosage unit.

35 In the case of oral administration, the oral dosage unit according to the invention is preferably a solid or semi-solid dosage form such as tablets, capsules, cachets, pellets, pills, powders and granules. The term "solid or semi-solid dosage form" also encompasses capsules that contain a liquid, e.g. an oil, in which the present estetrol component and/or the optional progestogenic component is dissolved or dispersed. Tablets and equivalent solid and semi-solid
40 dosage forms can suitably contain materials such as binders (e.g. hydroxypropylmethyl cellulose,

polyvinyl pyrrolidone, other cellulosic materials and starch), diluents (e.g. lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (e.g. starch polymers and cellulosic materials) and lubricating agents (e.g., stearates and talc). These tablets and equivalent solid dosage forms may be prepared by wet granulation, e.g. using an aqueous solution or an organic solution, as well as by direct compression.

In the case of sublingual, buccal or sublabial administration, the pharmaceutical composition according to the invention is preferable an orodispersible dosage unit.

The term "orodispersible dosage unit" as used herein refers to a dosage unit that is designed to rapidly disintegrate in the oral cavity when it comes into contact with saliva and to disperse the estetrol component into the saliva so it may be absorbed through the mucosal lining of the oral cavity.

When the patient still has a uterus, an optional progestogenic component may be administered in addition to the estetrol component.

Examples of progestogenic components which may suitably be used in accordance with the present invention include: levonorgestrel, norgestimate, norethisterone, dydrogesterone, drospirenone, 3-beta-hydroxydesogestrel, 3-ketodesogestrel, 17-deacetylnorgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, amgestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, fluorogestone acetate, gastrinone, gestodene, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol, mecirogestone, medroxyprogesterone, megestrol, megestrol, nomegestrol, norethindrone, norethynodrel, norgestrel (including d-norgestrel, and dl-norgestrel), norgestrienone, normethisterone, progesterone, quingestanol, (17 alpha)-17-hydroxy-11-methylene-19-norpregna-4, 15-dien-20-yn-3-one, tibolone, trimegestone, algestone-acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17alpha-ethynyltestosterone, 17alpha-ethynil-19-nortestosterone, d-17beta-acetoxy-13beta-ethyl-17alpha-ethynylgon-4-en-3-one oxime, 6beta, 7beta;15beta,16beta-dimethylene-3-oxo-17-pregna-4,9(11)-diene-21, 17beta-carbolactone or tanaproget and precursors of these compounds that are capable of liberating these progestogens in vivo when used in the present method.

Preferably the progestogenic component used in the present method is selected from the group consisting of progesterone, drospirenone, dydrogesterone, precursors of these progestogens and mixtures thereof.

When the progestogenic component of the invention is drospirenone, it is preferably used at a daily dose of from 0.5 mg to 10 mg, even more preferably of from 1 mg to 4 mg.

When the progestogenic component of the invention is dydrogesterone, it is preferably used at a daily dose of about 5 mg to about 10 mg, more preferably at a daily dose of about 5 mg.

When the progestogenic component of the invention is progesterone, it is preferably used at a daily dose of from 50 mg to 200 mg. In one embodiment, progesterone is used at a daily dose of 50 mg to 100 mg when it is used continuously. In another embodiment, progesterone is used at

a daily dose of 100 mg to 200 mg when it is used sequentially, for example when it is administered during about 14 days every month.

When a different progestogenic component is used, the daily dose is adjusted such as to
5 give the same pharmacological effect as a dose of 50 mg to 200 mg of progesterone.

In a preferred embodiment of the invention, the composition combines estetrol at a daily dose of about 20 mg with progesterone at a daily dose of about 100 mg.

10 In another embodiment of the invention, the estetrol component is administered to a patient who still has a uterus in conjunction with a Selective Estrogen Receptor Modulator (SERM), in particular in conjunction with bazedoxifene. Preferably bazedoxifene is administered at a daily dose of about 10 mg to 50 mg. More preferably, bazedoxifene is administered at a daily dose of about 20 mg.

15 The present invention has been described above with reference to a number of exemplary embodiments. Modifications and alternative implementations of some parts or elements are possible, and are included in the scope of protection as defined in the appended claims.

20

Examples

Example 1 - A Dose-Finding Study to Select the Daily Oral Dose of Estetrol (E4) for the Treatment of Vasomotor Symptoms in Post-Menopausal Women

25 Study enrolment and duration:

Enrolment was approximately 18 months. Individual subject participation was be up to 27 weeks: up to 6 weeks pre-screening and washout, up to 4 weeks screening and run-in period, up to 91 days (13 weeks) of E4/placebo treatment followed by 2 weeks (14 days) of progestin therapy and a Follow up visit 1 week after completion of progestin therapy in non-hysterectomised subjects only.

30

Primary Efficacy Objective:

To define the minimum effective dose (MED) of the oral dose of E4 by evaluating changes in frequency and in severity of moderate to severe vasomotor symptoms (VMS).

35 Methodology:

This was a prospective, multicentre, randomised, placebo-controlled, double-blinded, dose-finding study.

Subject Population:

40 Eligible subjects were hysterectomised and non-hysterectomised post-menopausal women aged

40 to 65 years, inclusive, presenting at least 7 moderate to severe hot flushes/day or at least 50 moderate to severe hot flushes/week.

Diagnosis and Inclusion Criteria:

- 5 The subjects have met all of the following inclusion criteria at the randomization visit. These criteria were assessed during the screening period:
1. Women aged 40 to 65 years, inclusive, presenting at least 7 moderate to severe hot flushes/day or at least 50 moderate to severe hot flushes/week in the week preceding randomization.
 2. Body Mass Index (BMI) between 18.0 and 35.0 kg/m², inclusive.
 - 10 3. Post-menopausal status defined as levels of follicle stimulating hormone (FSH) >40 IU/L and:
 - amenorrhoea for at least 12 consecutive months or,
 - amenorrhoea for at least 6 months with estradiol (E2) < 20 pg/mL or,
 - at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy with a copy of the pathology report or a statement on letterhead from the subject's physician documenting
 - 15 both ovaries were removed is required.
 4. For non-hysterectomised women: intact uterus with bi-layer endometrial thickness ≤5 mm on TVUS.
 5. Negative pregnancy test.
 6. Good physical and mental health, in the judgement of the Principal Investigator (PI), on the basis of medical, surgical and gynaecological history, physical examination, gynaecological examination, clinical laboratory, and vital signs.
 - 20 7. Subject has provided signed and dated written informed consent before admission to the study.
 8. Subject is able to understand and comply with the protocol requirements, instructions, and protocol-stated restrictions.

25

Exclusion Criteria:

Potential study subjects were excluded if one of the following exclusion criteria was present at the randomization visit. These criteria were assessed during the screening period:

1. For non-hysterectomised women: uterine disease or medical condition including :
 - 30 a. Bi-layer endometrial thickness >5mm as determined by TVUS;
 - b. Presence of fibroid(s) that obscure(s) evaluation of endometrium by TVUS;
 - c. History or presence of uterine cancer;
 - d. Presence of endometrial hyperplasia;
 - e. Presence of an endometrial polyp with hyperplastic or malignant epithelium.
- 35 2. Undiagnosed vaginal bleeding in the last 12 months.
3. Any history of malignancy with the exception of basal cell (excluded if within the prior 2 years) or squamous cell (excluded if within the prior one year) carcinoma of the skin. Any clinically significant findings at the breast examination and/or on mammography suspicious of breast malignancy that would require additional clinical testing to rule out breast cancer (however,
- 40 simple cysts confirmed by ultrasound were allowed). Note: A screening mammogram was

required unless the subject had a written documentation of a mammogram performed within the last 9 months.

4. Abnormal cervical Pap smear in non-hysterectomised subjects (written documentation of prior test within 18 months or test at screening exam) with evidence of cervical dysplasia greater than low grade squamous intraepithelial lesion (LSIL). Women with a diagnosis of atypical squamous cells of undetermined significance (ASCUS) were enrolled.
5. Systolic blood pressure (BP) outside the range 90 to 140 mmHg, diastolic BP outside the range 60 to 90 mmHg, and/or heart rate outside the range 40 to 100 bpm. Subjects with mild to moderate hypertension who were controlled on a stable antihypertension regimen were enrolled if they met the inclusion/exclusion criteria.
6. Any clinically significant abnormality identified on the screening 12-lead ECG.
7. History of venous or arterial thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, angina pectoris, etc.), history of known coagulopathy or abnormal coagulation factors.
8. Diabetes mellitus with poor glycaemic control in the last 6 months assessed by laboratory values of glucose outside the normal ranges and glycated haemoglobin above 7%.
9. Dyslipoproteinaemia predisposes the subject to atherosclerotic cardiovascular disease (ASCVD). If a subject had a 10 years ASCVD score $\geq 5\%$ as calculated using the ASCVD risk estimator (ACC/AHA Cardiovascular risk assessment guideline, 2013), she was not be included in the trial. In all cases, LDL cholesterol level ≥ 190 mg/dL or triglycerides plasma level > 400 mg/dL were exclusionary.
If a subject was receiving a lipid-lowering therapy, her treatment had to be on a stable dose for at least 1 month before screening and the same eligibility criteria had to be used.
10. Smoking >10 cigarettes/day or use of >1 ml/day of nicotine containing liquid for electronic cigarette.
11. Presence or history of gallbladder disease, unless cholecystectomy had been performed.
12. Systemic lupus erythematosus.
13. Multiple sclerosis.
14. Acute or chronic liver disease.
15. Acute or chronic renal impairment, including severe renal impairment.
16. Uncontrolled thyroid disorders.
17. Subject had a history of major depression or post-traumatic stress disorder (PTSD) within 2 years, OR a history of other major psychiatric disorder at any time (e.g., schizophrenia, bipolar disorder, etc.).
18. Use of oestrogen or progestin containing drug(s). A washout period is required before the Run-in Period in case of use of :
 - a. Vaginal hormonal products (rings, creams, gels) : washout of at least 4 weeks,
 - b. Transdermal oestrogen or oestrogen/progestin : washout of at least 4 weeks,
 - c. Oral oestrogen and/or progestin : washout of at least 4 weeks,
 - d. Intrauterine progestin therapy: washout of at least 4 weeks,

Current users of progestin implants or oestrogen alone injectable drug therapy were not allowed to participate unless the treatment was stopped more than 3 months ago. Current users of oestrogen pellet therapy or progestin injectable drug therapy were not allowed to participate unless the treatment was stopped more than 6 months ago.

- 5 19. Use of non-hormonal treatments to reduce hot flushes. A washout period of 1 week was required before the Run-in Period in the case of use of non-hormonal prescription and over-the-counter (OTC) treatments for hot flushes (such as anti-depressants paroxetine, escitalopram, venlafaxine, desvenlafaxine, and clonidine; or phytoestrogens, black cohosh, etc.). If one of these treatments was concomitantly taken with an oestrogen or progestin-containing drug, washout periods could be combined and did not have to be sequential.
- 10 20. Use of medication that may affect the outcome of the VMS endpoints within 28 days before the Run-in Period. This included (but was not limited to): SSRIs [selective serotonin reuptake inhibitors], SNRIs [serotonin and norepinephrine reuptake inhibitors], dopaminergic or antidopaminergic drugs, or gabapentin.
- 15 21. History or presence of allergy to the investigational product or drugs of this class, or history of drug or other allergy that, in the opinion of the Investigator contraindicated subject participation.
22. History or presence of allergy or intolerance to any component of the investigational product.
23. History of alcohol or substance abuse or dependence in the 12 months as determined by the Investigator, i.e. subject consumed excessive alcohol, abused drugs, or had a condition that could compromise the subject's ability to comply with study requirements in the Investigator's opinion.
- 20 24. Sponsor or Contract Research Organization (CRO) employees, or personnel in the department of the Investigator and relatives affiliated with this study.
- 25 25. Subjects with porphyria and subjects with known or suspected history of a clinically significant systemic disease, unstable medical disorders, life-threatening disease or current malignancies that would pose a risk to the subject in the opinion of the Investigator.
26. Participation in another investigational drug clinical study within 1 month (30 days) or had received an investigational drug within the last 3 months (90 days).
27. Was judged by the Investigator to be unsuitable for any reason.

30

Number of subjects:

Intention-To-Treat Principle

This principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

Further, the intention-to-treat principle implies that the primary analysis should include all randomised subjects.

Preservation of the initial randomisation in analysis is important in preventing bias and in providing a secure foundation for statistical tests. In many clinical trials the use of the full analysis set provides a conservative strategy. Under many circumstances it may also provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice.

5

In the present study, the Intention-To-Treat group included a total of 257 patients.

Subjects were randomly allocated to one of the 5 treatment arms in a 1:1:1:1:1 ratio. The randomisation was stratified by centre.

10 Study visits:

Week	Visit	Notation as used throughout all tables, listings and figures	Study part
Week -7 to -4	Visit 1 (Pre-Screening)	V1	Screening
Week -4 to -3	Visit 1a (Screening)	V1a	Screening
Week -1	Visit 2 (Baseline)	V2	Randomisation
Week 5	Visit 3	V3	Treatment period
Week 13	Visit 4 (EOT)	V4	End of treatment
Week 16	Visit 5 (EOS)	V5	End of study

Test Product and Reference Therapy, Dose, and Mode of Administration

All treatments (Estetrol, hereinafter E4, [2.5 mg, 5 mg, 10 mg, 15 mg] capsule) were administered once daily (QD) per os for at least 12 consecutive weeks until the last biological assessments (Day 91 maximum) had been performed.

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Placebo, 1 capsule administered QD per os for at least 12 consecutive weeks until the last biological assessments (Day 90 maximum) have been performed.

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If during the course of the trial, a double layer endometrial thickness ≥ 15 mm was detected on TVUS and/or abnormal uterine bleeding (in the judgement of the gynaecologist in light of the oestrogen therapy) was reported by a non-hysterectomised woman, she underwent an endometrial biopsy and was treated with progestin (10 mg dydrogesterone) QD until end of Week 11 in a sequential way (i.e., a 14 day progestin treatment period followed by a 14 day progestin treatment pause) in addition to the E4/placebo treatment. If the endometrial biopsy showed endometrial hyperplasia, the subject participation was immediately stopped and the treatment of hyperplasia was performed as per local guidelines. If an abnormal uterine bleeding occurred again after a first normal endometrial biopsy, a thorough gynaecological examination and a TVUS were performed. If necessary in the judgment of the gynaecologist, a second endometrial biopsy was performed.

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After the E4/Placebo treatment period, all non-hysterectomised subjects (including those having received the progestin previously) received progestin therapy for 14 days with 10 mg dydrogesterone QD.

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Results

A. Vasomotors parameters for each of the 5 treatment groups

- 5 1. Relative change (% from baseline) in weekly frequency of moderate to severe VMS
a) Week-by-week for each group

Week	2.5mg		5mg		10mg		15mg		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
1	-23%	23%	-23%	28%	-21%	29%	-22%	33%	-26%	25%
2	-34%	27%	-33%	29%	-37%	37%	-46%	34%	-41%	35%
3	-44%	29%	-38%	33%	-48%	39%	-57%	34%	-45%	33%
4	-49%	33%	-43%	34%	-55%	35%	-67%	30%	-49%	32%
5	-50%	33%	-47%	34%	-60%	33%	-72%	28%	-52%	32%
6	-54%	36%	-57%	31%	-65%	33%	-76%	26%	-56%	30%
7	-57%	36%	-57%	30%	-66%	34%	-79%	25%	-58%	30%
8	-58%	38%	-57%	32%	-68%	35%	-79%	26%	-58%	31%
9	-61%	36%	-59%	32%	-69%	36%	-81%	24%	-60%	31%
10	-61%	37%	-60%	32%	-70%	35%	-80%	27%	-63%	30%
11	-60%	39%	-63%	31%	-70%	34%	-82%	25%	-65%	31%
12	-61%	38%	-62%	32%	-72%	33%	-84%	23%	-65%	30%

- 10 In order to better analyse the data recorded in this study, treatment groups have been compared using an ANCOVA (analysis of covariance) with respect to the change in weekly frequency of moderate to severe VMS from baseline to week 4 and 12. The ANCOVA model includes treatment ("trt1") and study centre ("SITEPOOL") as a fixed effect and baseline ("base") as a covariate.

- 15 b) Covariate significance

The Table below presents a comparison over all treatment groups.

Analysis Timepoint (N)	Covariate	p_value
4	trt1	0.0147
4	base	0.3684
4	SITEPOOL	0.3236
12	trt1	0.0100
12	base	0.1490
12	SITEPOOL	0.0958

c) The Table below presents pairwise comparisons with placebo:

<i>Analysis Timepoint (N)</i>	<i>Planned treatment (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>
4	0	-0.49080693	-0.578953	-0.402661
4	2.5	-0.48482309	-0.576836	-0.392811
4	5	-0.42247695	-0.517552	-0.327402
4	10	-0.54456428	-0.634678	-0.454450
4	15	-0.64721795	-0.741703	-0.552733
12	0	-0.64237949	-0.726371	-0.558388
12	2.5	-0.60565210	-0.693328	-0.517976
12	5	-0.60259514	-0.693189	-0.512001
12	10	-0.70041629	-0.786283	-0.614549
12	15	-0.80089486	-0.890927	-0.710863

All statistical tests are supported by presenting Least Square adjusted mean (LS adjusted mean: the group means after having controlled for a covariate; also referred to as marginal means or estimated marginal means) and 95% confidence intervals for the respective treatment effects. These LS adjusted means and Confidence Intervals are based on the statistical models used for the analysis.

The Confidence Intervals implies that if the same population is sampled on numerous occasions and interval estimates are made on each occasion, the resulting intervals would bracket the true population parameter in approximately 95 % of the cases.

d) The Table below presents differences with placebo:

<i>Analysis Timepoint (N)</i>	<i>Higher dose (mg)</i>	<i>Lower dose (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>	<i>p_value</i>
4	2.5	0	0.005984	-0.152112	0.164079	0.99995
4	5.0	0	0.068330	-0.092296	0.228956	0.68478
4	10.0	0	-0.053757	-0.209916	0.102401	0.81738
4	15.0	0	-0.156411	-0.315800	0.002977	0.05622
12	2.5	0	0.036727	-0.113917	0.187372	0.93696
12	5.0	0	0.039784	-0.113271	0.192840	0.92218
12	10.0	0	-0.058037	-0.206836	0.090762	0.74506
12	15.0	0	-0.158515	-0.310392	-0.006639	0.03771

From this Table it can be seen that the 15 mg daily dose generates a statistically significant difference with placebo at 12 weeks (p-value of 0.03771) and an almost statistically significant difference with placebo at 4 weeks (p-value of 0.05622).

It is particularly striking to observe the low p-values obtained for the 15 mg dose by comparison to the elevated p-values obtained for the 10 mg dose.

2. Relative change (% from baseline) in Hot Flush Weekly Weighted Score

a) Week-by-week for each group

Week	2.5mg		5mg		10mg		15mg		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
1	-24%	22%	-23%	28%	-20%	28%	-22%	32%	-25%	26%
2	-33%	26%	-32%	29%	-34%	36%	-45%	32%	-40%	34%
3	-43%	28%	-38%	32%	-46%	39%	-56%	32%	-44%	32%
4	-47%	33%	-43%	34%	-53%	34%	-66%	29%	-48%	31%
5	-48%	33%	-47%	35%	-57%	32%	-70%	27%	-51%	31%
6	-51%	36%	-56%	30%	-62%	32%	-72%	26%	-56%	29%
7	-52%	34%	-56%	29%	-64%	32%	-75%	25%	-57%	29%
8	-54%	37%	-56%	30%	-66%	34%	-76%	26%	-57%	30%
9	-56%	34%	-58%	31%	-66%	34%	-78%	25%	-58%	30%
10	-56%	35%	-59%	31%	-68%	34%	-77%	27%	-62%	30%
11	-56%	37%	-61%	30%	-68%	33%	-79%	26%	-63%	30%
12	-56%	36%	-60%	32%	-69%	32%	-81%	24%	-64%	29%

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b) Covariate significance

<i>Analysis Timepoint (N)</i>	<i>Covariate</i>	<i>p_value</i>
4	trt1	0.0178
4	base	0.5039
4	SITEPOOL	0.3748
12	trt1	0.0045
12	base	0.1059
12	SITEPOOL	0.0442

c) Pairwise comparisons with placebo:

<i>Analysis Timepoint (N)</i>	<i>Planned treatment (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>
4	0	-0.47565366	-0.562163	-0.389145
4	2.5	-0.46123761	-0.550786	-0.371689
4	5	-0.41965751	-0.513022	-0.326293
4	10	-0.51383409	-0.602253	-0.425415
4	15	-0.63218069	-0.724860	-0.539501
12	0	-0.63439437	-0.715652	-0.553137
12	2.5	-0.55001195	-0.634124	-0.465900
12	5	-0.58606503	-0.673762	-0.498368
12	10	-0.67674243	-0.759794	-0.593691
12	15	-0.76883426	-0.855888	-0.681781

d) Differences with placebo

<i>Analysis Timepoint (N)</i>	<i>Higher dose (mg)</i>	<i>Lower dose (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>	<i>p_value</i>
4	2.5	0	0.014416	-0.139707	0.168539	0.99815
4	5.0	0	0.055996	-0.101685	0.213678	0.80079
4	10.0	0	-0.038180	-0.191319	0.114958	0.93202
4	15.0	0	-0.156527	-0.313119	0.000065283	0.05013
12	2.5	0	0.084382	-0.060384	0.229149	0.41549
12	5.0	0	0.048329	-0.099780	0.196438	0.84302
12	10.0	0	-0.042348	-0.186190	0.101493	0.88450
12	15.0	0	-0.134440	-0.281526	0.012646	0.08430

- 5 From this Table it can be seen that the 15 mg daily dose generates a statistically significant difference with placebo at 4 weeks (p-value of 0.05013) and an almost statistically significant difference with placebo at 12 weeks (p-value of 0.08430).

It is particularly striking to observe the low p-values obtained for the 15 mg dose by comparison to the elevated p-values obtained for the 10 mg dose.

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B. Vasomotors parameters for the 10 mg and 15 mg groups by comparison to the placebo and inefficient doses (2.5 mg and 5 mg) grouped together

Based on the results observed in section A above, it became apparent that the two lowest doses tested (2.5 mg per day and 5 mg per day) did not show efficacy. A further analysis of the results was thus prepared, where data from these two doses were grouped with the placebo dose and compared to the 10 mg and 15 mg doses.

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1. Relative change (% from baseline) in weekly frequency of moderate to severe VMS

a) Week-by-week for each group

Week	10mg		15mg		Placebo with 2.5 and 5 mg	
	Mean	SD	Mean	SD	Mean	SD
0	0%	0%	0%	0%	0%	0%
1	-21%	29%	-22%	33%	-24%	25%
2	-37%	37%	-46%	34%	-35%	31%
3	-48%	39%	-57%	34%	-42%	32%
4	-55%	35%	-67%	30%	-47%	33%
5	-60%	33%	-72%	28%	-50%	33%
6	-65%	33%	-76%	26%	-56%	32%
7	-66%	34%	-79%	25%	-58%	32%
8	-68%	35%	-79%	26%	-58%	34%
9	-69%	36%	-81%	24%	-60%	33%
10	-70%	35%	-80%	27%	-61%	33%
11	-70%	34%	-82%	25%	-63%	34%
12	-72%	33%	-84%	23%	-63%	33%

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b) Covariate significance

<i>Analysis Timepoint (N)</i>	<i>Covariate</i>	<i>p_value</i>
4	trt1	0.0039
4	base	0.3935
4	SITEPOOL	0.3308
12	trt1	0.0017
12	base	0.1244
12	SITEPOOL	0.0957

c) Pairwise comparisons with placebo (including ineffective doses 2.5 mg and 5 mg)

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<i>Analysis Timepoint (N)</i>	<i>Planned treatment (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>
4	0	-0.46779276	-0.521579	-0.414007
4	10	-0.54424142	-0.634204	-0.454279
4	15	-0.64752092	-0.741851	-0.553191
12	0	-0.61799510	-0.669162	-0.566828
12	10	-0.70075417	-0.786337	-0.615172
12	15	-0.80058459	-0.890322	-0.710847

d) Differences with placebo (including ineffective doses 2.5 mg and 5 mg)

<i>Analysis Timepoint (N)</i>	<i>Higher dose (mg)</i>	<i>Lower dose (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>	<i>p_value</i>
4	10.0	0	-0.076449	-0.193421	0.040523	0.26148
4	15.0	0	-0.179728	-0.301777	-0.057679	0.00218
12	10.0	0	-0.082759	-0.194036	0.028518	0.17979
12	15.0	0	-0.182589	-0.298696	-0.066483	0.00099

- 5 As already mentioned under A)1)d) above it is particularly striking to observe the low p-values obtained for the 15 mg daily dose by comparison to the elevated p-values obtained for the 10 mg daily dose demonstrating the unique relief obtained with the 15 mg daily dose.

2. Relative change (% from baseline) in Hot Flush Weekly Weighted Score:

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a) Week-by-week for each group

Week	10mg		15mg		Placebo with 2.5 and 5 mg	
	Mean	SD	Mean	SD	Mean	SD
0	0%	0%	0%	0%	0%	0%
1	-20%	28%	-22%	32%	-24%	25%
2	-34%	36%	-45%	32%	-36%	30%
3	-46%	39%	-56%	32%	-42%	31%
4	-53%	34%	-66%	29%	-46%	32%
5	-57%	32%	-70%	27%	-49%	33%
6	-62%	32%	-72%	26%	-54%	32%
7	-64%	32%	-75%	25%	-55%	31%
8	-66%	34%	-76%	26%	-56%	32%
9	-66%	34%	-78%	25%	-57%	31%
10	-68%	34%	-77%	27%	-59%	32%
11	-68%	33%	-79%	26%	-60%	33%
12	-69%	32%	-81%	24%	-60%	32%

b) Covariate significance

<i>Analysis Timepoint (N)</i>	<i>Covariate</i>	<i>p_value</i>
4	trt1	0.0037
4	base	0.5294
4	SITEPOOL	0.3783
12	trt1	0.0015
12	base	0.0770
12	SITEPOOL	0.0487

5 c) Pairwise comparisons with placebo (including ineffective doses 2.5 mg and 5 mg)

<i>Analysis Timepoint (N)</i>	<i>Planned treatment (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>
4	0	-0.45362100	-0.506219	-0.401023
4	10	-0.51368261	-0.601866	-0.425499
4	15	-0.63242707	-0.724866	-0.539989
12	0	-0.59132448	-0.640861	-0.541788
12	10	-0.67757463	-0.760625	-0.594524
12	15	-0.76832743	-0.855386	-0.681269

d) Differences with placebo (including ineffective doses 2.5 mg and 5 mg)

<i>Analysis Timepoint (N)</i>	<i>Higher dose (mg)</i>	<i>Lower dose (mg)</i>	<i>LS adjusted mean</i>	<i>Lower 95% confidence limit</i>	<i>Upper 95% confidence limit</i>	<i>p_value</i>
4	10.0	0	-0.060062	-0.174760	0.054636	0.41666
4	15.0	0	-0.178806	-0.298114	-0.059498	0.00178
12	10.0	0	-0.086250	-0.194272	0.021772	0.14044
12	15.0	0	-0.177003	-0.289367	-0.064639	0.00097

As already mentioned under A)2)d) and even more strongly supported here with the data shown in this Table, it can be seen that the 15 mg daily dose generates a statistically significant difference with placebo at 4 weeks (p-value of 0.00178) and at 12 weeks (p-value of 0.00097). Again, it is particularly striking to observe the low p-values obtained for the 15 mg dose by comparison to the elevated p-values obtained for the 10 mg dose.

C. Menopause Rating Scale

The Menopause Rating Scale (MRS) is a health-related quality of life scale allowing the measure of severity of age-/menopause-related complaints by rating a profile of symptoms (Heinemann et al., 2003, "*International versions of the Menopause Rating Scale (MRS)*" Health Qual Life Outcomes 1: 28; Heinemann et al., 2004, "*The Menopause Rating Scale (MRS) scale: A methodological review*". Health Qual Life Outcomes 2: 45; Heinemann et al., 2004, "*The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study*". Health Qual Life Outcomes 2:67).

The score increases point by point with increasing severity of subjectively perceived complaints in each one of 11 items (severity expressed in 0 to 4 points in each item). By checking these 5 possible boxes of "severity" for each of the items in the questionnaire, the respondent provides her personal perception. The total MRS score ranges between 0 (asymptomatic) to 44 (highest degree of complaints). The minimal/maximal scores vary between three dimensions depending on the number of complaints allocated to the respective dimension of symptoms (Heinemann et al., 2003, Health Qual Life Outcomes 1: 28):

1. psychological symptoms: 0 to 16 scoring points (4 symptoms: depressed, irritable, anxious, exhausted);
2. somato-vegetative symptoms: 0 to 16 points (4 symptoms: sweating/flush, cardiac complaints, sleeping disorders, joint & muscle complaints);
3. urogenital symptoms: 0 to 12 points (3 symptoms: sexual problems, urinary complaints, vaginal dryness).

Total MRS Score

Week	2.5mg		5mg		10mg		15mg		Placebo	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	16.5	7.2	16.5	7.3	17.6	7.6	16.4	8.1	18.2	8.9
Week 4	10.3	5.6	10.5	6.7	11.7	6.8	8.7	6.2	12.8	8.0
Week 12	9.5	6.7	11.0	7.7	9.7	6.9	8.1	5.8	11.4	7.8

The Menopause Rating Scale (MRS) points to an overall improvement in quality of life, with the strongest effect for the 15 mg dose. At this dose, a near statistically significant effect was observed, with a p-value of 0.07.

D. Measurements related to treatment side effects

1. Number of patient with biopsies

Treatment Group	Placebo	2.5 mg	5 mg	10 mg	15 mg
Number of patients with biopsies	4	4	5	11	9

2. Adverse Events (AEs)

Treatment Group	Placebo	2.5 mg	5 mg	10 mg	15 mg
Count of Treatment Emergent AEs (TEAEs)	71	61	63	95	82
Percentage of patients with severe TEAE	9.1	7.7	10.6	7.4	6.1
Percentage of patients with TEAE leading to Study Discontinuation	3.6	1.9	6.4	5.6	4.1

It can be seen from the Tables above that the patients in the 15 mg group present less TEAEs than patients in the 10 mg group. In the 10 mg group of patients who had AEs, the average was 3.2 AEs per patient. By comparison, in the 15 mg group, patients who had AEs had on average 2.6 AEs. Globally, those data show that the 15 mg daily dose provides a significant relief of hot flushes without generating additional AEs for the patients. In addition, there were less requirements for biopsies in the 15 mg per day group than in the 10 mg per day group.

3. Patients leaving the study

Treatment Group	Placebo	2.5 mg	5 mg	10 mg	15 mg
Number of patients leaving the study	14	9	11	15	8

E. Measurements performed at 15 mg and 20 mg daily doses

In order to better assess the potential for increasing the daily dose beyond the minimum effective dose of 15 mg daily, a number of parameters were followed in a study where estetrol was administered at the increased dose of 20 mg per day.

1. Triglycerides level (mmol/L)

Treatment	Parameter	Baseline	End Of Treatment *	
			Actual Value	Actual Change from Baseline
E4 15 mg	Mean	1.32	1.61	0.20
	SD	0.64	0.94	0.82
	Median	1.21	1.40	0.15
E4 20 mg	Mean	1.43	1.53	0.10
	SD	0.47	0.63	0.44
	Median	1.40	1.40	0.10

* End Of Treatment was after 28 days for the 20 mg dose and after 12 weeks for the 15 mg dose.

2. Glucose level (mmol/L)

Treatment	Parameter	Baseline	End Of Treatment *	
			Actual Value	Actual Change from Baseline
E4 15 mg	Mean	5.10	4.79	0.02
	SD	0.73	0.58	0.56
	Median	4.94	4.77	0.05
E4 20 mg	Mean	5.53	5.44	-0.10
	SD	0.54	0.50	0.22
	Median	5.60	5.60	-0.15

* End Of Treatment was after 28 days for the 20 mg dose and after 12 weeks for the 15 mg dose.

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3. Cholesterol level (mmol/L)

Treatment	Parameter	Baseline	End Of Treatment *	
			Actual Value	Actual Change from Baseline
E4 15 mg	Mean	5.51	5.63	0.12
	SD	0.83	0.97	0.73
	Median	5.62	5.71	0.08
E4 20 mg	Mean	6.27	6.09	-0.18
	SD	0.90	0.96	0.65
	Median	6.25	6.10	-0.20

* End Of Treatment was after 28 days for the 20 mg dose and after 12 weeks for the 15 mg dose.

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4. HDL-cholesterol level (mmol/L)

Treatment	Parameter	Baseline	End Of Treatment *	
			Actual Value	Actual Change from Baseline
E4 15 mg	Mean	1.73	1.89	0.16
	SD	0.46	0.41	0.24
	Median	1.66	1.81	0.17
E4 20 mg	Mean	1.68	1.97	0.29
	SD	0.37	0.36	0.14
	Median	1.60	1.90	0.35

* End Of Treatment was after 28 days for the 20 mg dose and after 12 weeks for the 15 mg dose.

5.LDL-cholesterol level (mmol/L)

Treatment	Parameter	Baseline	End Of Treatment *	
			Actual Value	Actual Change from Baseline
E4 15 mg	Mean	3.05	3.14	0.09
	SD	0.85	0.95	0.45
	Median	3.22	3.25	0.10
E4 20 mg	Mean	3.94	3.43	-0.51
	SD	0.98	1.05	0.56
	Median	4.00	3.45	-0.65

* End Of Treatment was after 28 days for the 20 mg dose and after 12 weeks for the 15 mg dose.

5

From the above 5 Tables it can be observed that these lipid parameters and glucose level do not behave significantly differently when a 20 mg daily dose is used in place of a 15 mg daily dose.

6.C-terminal telopeptide (CTX-1) (ng/L)

Treatment	Parameter	Baseline	End Of Treatment *	
			Actual Value	Actual Change from Baseline
E4 15 mg	Mean	416.0	320.9	-95.0
	SD	286.16	359.65	442.18
	Median	339.0	197.5	-142.5
E4 20 mg	Mean	422.50	274.9	-147.60
	SD	134.8	95.3	70.6
	Median	416.5	267.50	-138.0

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* End Of Treatment was after 28 days for the 20 mg dose and after 12 weeks for the 15 mg dose.

CTX-1 is a specific marker of bone resorption.

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In the Table above it can be seen that the 15 mg daily dose leads to a small decrease of bone resorption and this effect is more pronounced with the 20 mg daily dose already after 28 days of treatment.

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It is thus reasonable to envision a hormone replacement therapy for alleviating menopause-associated symptoms which uses a daily dose of estetrol of between 15 mg, the minimal effective dose, and 20 mg, or even 25 mg which, by extension of the above data, will allow a better benefit-

to-risk profile to be obtained. Increasing the estetrol dose beyond the minimal effective dose of 15 mg per day will indeed offer even better efficacy in VMS relief and in parameters such as bone resorption, while maintaining an excellent safety profile (including, but not limited to, Adverse Events, as presented under Section D)2) above, and particularly lipid parameters and glucose level

5 presented under Section E) 1) to 5) above. Increasing the estetrol dose beyond the minimal effective dose of 15 mg per day will also permit a faster onset of relief to be obtained when patients initiate hormone replacement therapy.

Claims

1. A composition for use in alleviating menopause-associated symptoms, wherein said composition comprises an estetrol component in a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.
- 5 2. The composition for use of Claim 1 wherein a second composition comprising a progestogenic component is used.
3. The composition for use of Claim 2 wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone.
4. The composition for use of Claim 2 wherein progesterone is used at a daily dose of from
10 50 mg to 200 mg.
5. The composition for use of Claim 1 wherein a second composition comprising bazedoxifene is used.
6. A composition for use according to any one of Claims 2-5 wherein said second composition comprising a progestogenic component or bazedoxifene is the same as the composition
15 comprising the estetrol component.
7. A composition for use according to any one of Claims 1-6 wherein the estetrol component is estetrol, preferably estetrol monohydrate.
8. A composition for use according to any of the preceding claims wherein the composition is formulated as an oral dosage unit.
- 20 9. The composition for use according to Claim 8 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

Abstract

The present invention relates to a hormone replacement therapy for alleviating menopause-associated symptoms which is based on the administration to a female mammal of an estetrol
5 component at specified daily doses, optionally in combination with a progestogenic component.

The therapy enjoys a statistically significant efficacy combined with a favourable profile for side effects compared to currently available methods for alleviating menopause-associated symptoms.