# A Multicentre Dose-Finding, Randomised, Double-Blind, Placebo-Controlled Study to Select the Daily Oral Dose of Estetrol (E4) for the Treatment of Vasomotor Symptoms in Post-Menopausal Women

Published: 03-02-2016
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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) within each treatment arm at week 4 and 12. Secondary…

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Menopause related conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46289

**Source**
ToetsingOnline

**Brief title**
E4 RELIEF

### Condition

- Menopause related conditions

**Synonym**
Menopausal Symptoms, Vasomotor Symptoms

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Donesta Bioscience B.V. (attn. Mrs. Francoise Bruyère)
**Source(s) of monetary or material Support:** Donesta Bioscience

## Intervention

**Keyword:** Estetrol, Post-Menopausal, Vasomotor Symptoms, Women

## Outcome measures

### Primary outcome

Primary Efficacy Variables:

There are 4 co-primary efficacy variables:

1. Change in weekly frequency of moderate to severe VMS from baseline to week 4.

2. Change in weekly frequency of moderate to severe VMS from baseline to week

12.

3. Change in severity of moderate to severe VMS from baseline to week 4.

4. Change in severity of moderate to severe VMS from baseline to week 12.

The Severity Scoring System of VMS will be documented by the subjects in the

diary by using the following scores:

None (0) = no VMS symptoms

Mild (1) = Sensation of heat without sweating

Moderate (2) = Sensation of heat with sweating. Able to continue activity

Severe (3) = Sensation of heat with sweating. Causes cessation of activity.

### Secondary outcome

Secondary Efficacy Variables:

Change from baseline to week 13 in the following GSM symptoms (VVA subject

self- assessment).

* Vaginal dryness (none, mild, moderate or severe),

* Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe),

* Dysuria (none, mild, moderate or severe),

* Vaginal pain associated with sexual activity (none, mild, moderate or severe),

* Vaginal bleeding associated with sexual activity (presence vs. absence).

The self-assessment of VVA is done at the baseline/Visit 2 and end of treatment (EOT)/Visit 4.

Change from baseline to week 5 and week 13 in Menopause Rating Scale (MRS)

The scoring increases point by point with increasing severity of subjectively perceived complaints in each of the 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 the respondent provides her personal perception. The total score of the MRS ranges between 0 (asymptomatic) to 44 (highest degree of complaints). The minimal/maximal scores vary between the three dimensions depending on the number of complaints allocated to the respective dimension of symptoms:

* psychological symptoms: 0 to 16 scoring points ( 4 symptoms: depressed, irritable, anxious, exhausted)

* somato-vegetative symptoms: 0 to 16 points (4 symptoms: sweating/flush, cardiac complaints, sleeping disorders, joint & muscle complaints)

* urogenital symptoms: 0 to 12 points (3 symptoms: sexual problems, urinary complaints, vaginal dryness).

The MRS is completed at the baseline/Visit 2, treatment period/Visit 3 and end

of treatment (EOT)/Visit 4.

Change from baseline to week 13 in Vaginal pH

Performed on-site by an Investigator or qualified site personnel using a standardized vaginal pH paper test at baseline/Visit 2 and EOT/Visit 4.

Change from baseline to week 13 in Vaginal MI (parabasal and superficial cells)

Samples are taken during the course of obtaining a vaginal cytology (baseline/Visit 2 and EOT/Visit 4). A MI is a ratio obtained through performing a random count of three major cell types (parabasal cells, intermediate cells and superficial cells) that are shed from the squamous epithelium. The cell count is expressed as a percentage that reads as follows: MI= % parabasal cells, % intermediate cells, % superficial cells.

Change from baseline to week 13 in lipid and glucose metabolism markers, haemostatic variables and bone variables (triglycerides, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol, total cholesterol, fasting glycaemia, insulin, glycated haemoglobin and homeostasis model assessment-estimated insulin resistance [HOMA-IR]; prothrombin fragment 1 + 2, endogenous thrombin potential [ETP]-based activated protein C sensitivity ratio(APCsr ETP) , D-dimers, sex hormone-binding globulin [SHBG], anti-thrombin, Protein-C, free Protein-S, Factor VIII, free Tissue factor pathway inhibitor [TFPI], osteocalcin and C-terminal telopeptide [CTX-1]).

Blood samples will be taken for identifying change in lipids/lipoproteins, glucose metabolism markers, haemostatic variables and bone variables at baseline/Visit 2 and EOT/Visit 4.

Pharmacokinetic (PK)

Blood samples will be taken for evaluating E4 concentrations at baseline (baseline/Visit 2) and steady state (treatment period/Visit 3 and EOT/Visit 4).

Safety Variables

For non-hysterectomised subjects, bi-layer endometrial thickness is evaluated by TVUS (change of endometrial thickness) and bleeding pattern by daily diary recording. Other safety parameters including adverse event (AE) monitoring, physical and gynaecological examination (including vital signs and breast examination), electrocardiogram (ECG), routine clinical laboratory tests (e.g. haematology and chemistry) are evaluated in both hysterectomised and non-hysterectomised subjects.

# Study description

**Background summary**

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 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, Speroff et al. 2005). Most experience hot flushes for about two years, although around 10% suffer for more than 10 years (Rodstrom, Bengtsson et al. 2002). 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). The epithelial linings of the vagina and urethra are very sensitive to oestrogen, and 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.

**Study objective**

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) within each treatment arm at week 4 and 12.

Secondary Efficacy Objective: To evaluate effects of different doses of E4 on genitourinary syndrome of menopause (GSM) also called vulvovaginal atrophy (VVA), on vaginal maturation index (MI), on vaginal pH, on change in the Menopause Rating Scale (MRS), on lipid and glucose metabolism, on haemostatic and bone laboratory variables, and E4 concentrations at baseline and steady state.

Safety Objective: To evaluate safety in non-hysterectomised subjects by monitoring transvaginal ultrasonography (TVUS) change of endometrial thickness at each study visit during the E4/placebo treatment period and by daily diary entry for bleeding pattern. To evaluate safety in both hysterectomised and non-hysterectomised subjects by (serious) adverse event ([S]AE) monitoring, physical and gynaecological examination (including vital signs and breast examination), electrocardiogram (ECG), routine clinical laboratory tests (e.g. haematology and chemistry).

**Study design**

Subjects will be randomly allocated to either treatment group (2,5 mg E4, 5 mg E4, 10 mg E4, 15 mg E or placebo) in a 1:1:1:1:1 ratio. The randomisation will be stratified per centre.

All treatments (E4 or Placebo) will be administered once daily (QD) per os for at least 12 consecutive weeks until the last biological assessments (Day 91 maximum) have been performed. After the E4/placebo treatment period, non-hysterectomised subjects only will receive progestin therapy for 14 days with 10 mg dydrogesterone QD.

The study consists of 5 study visits. A washout period (typically 1 to 4 weeks) is required before the run-in period in case of prior use of oestrogen or progestin-containing drugs.

## Intervention

All treatments including placebo will be administered, 1 capsule administered QD per os (Group 1) for at least 12 consecutive weeks until the last biological assessments (Day 91 maximum) have been performed.

After the E4/placebo treatment period, non-hysterectomised subjects only will receive progestin therapy for 14 days with 10 mg dydrogesterone QD.

## Study burden and risks

Please refer to page 31 onwards in the protocol.

There will be 5 study visits: Visit 1 (Pre-screening and Washout, up to 4 weeks prior to Screening); Visit 1a (Screening visit up to 1 week prior to the Run-In period); Visit 2 (Randomization and Baseline Assessment, Day -1), Visit 3 (Week 5), Visit 4 (End of treatment [EOT]/Week 13) and Visit 5 (End of study [EOS]/Week 16).

After screening, subjects will have a 2-week Run-In period (Day -15 to Day -2) during which they will record their hot flushes each day in an electronic diary (e-diary). After Visit 4, the last 3 weeks of diary completion will only include bleeding assessment using the scale provided in the section 8.2.3 of the protocol. Hot flushes and pill intake will not need to be recorded.

Subject will document the intake of the investigational drug product in an e-diary (e-diary).

Gyn. examiniaton at screening (visit 1a), End of Treatment (visit 4) and End of Study / Follow Up (visit 5).
Cervical Pap smear at screening.
Urin Pregnancy Test at screening.
TVUS at screening, visit 2, visit 3, visit 4 and visit 5.
Breast Examination at screening, visit 4 and visit 5.
Mammography at screening unless a normal result is available within 9 months before study start.
Self Assessment of VVA (vulvovaginal) symptoms at visit 2, visit 4.
ECG at visit 1a, visit 4.
Routine urinalysis, visit 1a, visit 4.
Fasten blood sampling at visit 1a, visit 2, visit 3, visit 4, visit 5.

Benefits of HRT are that it is the best therapy for relief of hot

flashes/flushes and night sweats as well as for vaginal dryness and atrophic changes. Additionally, it has dose-related benefit for bone health and for prevention of osteoporosis. HRT also has been shown to enhance libido and quality of life. Lastly, HRT can be administered via multiple routes (oral, transdermal, injection, intra-uterine, vaginal) and can thus be based on personal preference for most women who require this treatment.

Risks of HRT include oestrogen-dependent endometrial neoplasia; however, combination HRT (oestrogen plus progestin) can nearly completely eliminate this risk. There is increased risk for breast neoplasia when combination HRT is continually used for 5 or more years; however, a risk is not currently associated with oestrogen-only therapy, although these data are controversial. Currently, there is also conflicting data suggesting an increased risk for ovarian neoplasia after 5 years of HRT. Other risks include breast tenderness and swelling.

There is a low risk for thromboembolic disease; however, this risk increases with age and other risk factors (e.g., cardiovascular disease, obesity, fracture, renal disease, congenital and acquired thrombophilic disorders, smoking). Induction or exacerbation of hypertension has also been found in a few women although HRT is typically associated with reducing hypertension. Women with cardiovascular disease should not initiate or continue HRT for primary or secondary prevention of coronary artery disease. Currently, there is insufficient evidence to claim that prolonged HRT improves cardiovascular outcomes and there may be an increased risk of stroke.
Other minor risks include vaginal bleeding secondary to endometrial stimulation which may be mitigated with progestin therapy; nausea or vomiting also has been noted in a small percentage of women.

Contraindications include undiagnosed genital bleeding; known or suspected oestrogen-dependent neoplasm (risk of use in survivors not known); active deep vein thrombosis, pulmonary embolism or a history of these; active or recent arterial thromboembolic disease (stroke or myocardial infarction); liver dysfunction or disease; known or suspected pregnancy; and women who may have hypersensitivity to HRT preparations.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

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.
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 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.
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.

## Exclusion criteria

1. For non-hysterectomised women: uterine disease or medical condition including :
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.
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, simple cysts confirmed by ultrasound are allowed). Note: A screening mammogram is required unless the subject has 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) may be 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 are controlled on a stable antihypertension regimen may be enrolled if they meet 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%. Ranges will be provided in the study specific site laboratory manual.
9. Dyslipoproteinaemia predisposes the subject to atherosclerotic cardiovascular disease (ASCVD). If a subject has a 10 years ASCVD score * 5% as calculated using the ASCVD risk estimator (ACC/AHA Cardiovascular risk assessment guideline, 2013), she may not be included in the trial. In all cases, LDL cholesterol level * 190 mg/dL or triglycerides plasma level > 400 mg/dL is exclusionary.
If a subject is receiving a lipid-lowering therapy, her treatment has to be on a stable dose for at least 1 month before screening and the same eligibility criteria has 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 has 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 has 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 are 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 are not allowed to participate unless the treatment was stopped more than 6 months ago.
19. Use of non-hormonal treatments to reduce hot flushes. A washout period of 1 week is 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.). Note that if one of these treatments is concomitantly taken with an oestrogen or progestin-containing drug, washout periods can be combined and must not be sequential.
20. Use of medication that may affect the outcome of the VMS endpoints within 28 days before the Run-in Period. This includes (but is not limited to): SSRIs [selective serotonin reuptake inhibitors], SNRIs [serotonin and norepinephrine reuptake inhibitors], dopaminergic or antidopaminergic drugs, or gabapentin.
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 contraindicates 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 consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject*s ability to comply with study requirements in the Investigator*s opinion.
24. Sponsor or Contract Research Organization (CRO) employees, or personnel in the department of the Investigator and relatives affiliated with this study.
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 have received an investigational drug within the last 3 months (90 days).
27. Is judged by the Investigator to be unsuitable for any reason.

## Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Prevention |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-04-2016 |
| Enrollment: | 34 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | N/A |
| Generic name: | Estetrol (E4) |

# Ethics review

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|---|---|
| Approved WMO Date: | 03-02-2016 |
| Application type: | First submission |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 22-03-2016 |
| Application type: | First submission |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 26-08-2016 |

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|---|---|
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 30-08-2016 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 29-03-2017 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 21-04-2017 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 09-06-2017 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 13-07-2017 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015-004018-44-NL |
| ClinicalTrials.gov | NCT02834312 |
| CCMO | NL55895.072.16 |