STUDY SYNOPSIS

NAME OF SPONSOR Estetra SRL	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Estetrol (E4)		
NAME OF ACTIVE INGREDIENT Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol		

TITLE OF THE STUDY

A feasibility study into the contraceptive effect of estetrol (E4) alone or combined with either progesterone (P4) or desogestel (DSG) by daily oral administration to healthy female volunteers for 28 days.

PRINCIPAL INVESTIGATORS

[redacted]

Publications

- Visser M, Coelingh Bennink HJT. Clinical applications for estetrol. J Steroid Biochem Mol Biol.2009;114(1-2):85-9. DOI: 10.1016/j.jsbmb.2008.12.013.
- Visser, M, Coelingh Bennink HJT. Estetrol, the new natural estrogen for clinical use in women. Ref Gynecol Obstet.2011;14:427-32.

PHASE OF DEVELOPMENT

Phase IIA

STUDY PERIOD

The first subject was randomized on January 21, 2008 and the last subject completed the study on August 4, 2008. The recruitment period was 7 months and the total study period covered 10 months.
The first intake of study medication took place on January 27, 2008 and the last intake on July 14, 2008.

STUDY OBJECTIVES

- To investigate ovarian suppression and ovulation inhibition
- To evaluate hypothalamic-pituitary-ovarian (HPO) function
- Pharmacokinetics (PK) of E4
- Safety and tolerability

METHODOLOGY

This was an open-label feasibility study with 4 treatment groups. Stratification was performed based on the day ovulation occurred in the pre-treatment cycle.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)

Planned: 50; Randomized: 52 (3 subjects dropped-out from the clinical study)

Analysis sets	Safety population	Efficacy population
TOTAL	**52**	**51**
10 mg E4	10	10
20 mg E4	11	10
20 mg E4/150 µg DSG	15	15
20 mg E4/200 mg P4	16	16

MAIN CRITERIA FOR INCLUSION

- At least 18 years and not older than 40 years of age
- Willing to use a barrier method of contraception during the total study period.
- Ovulation in the pre-treatment cycle ≤ day 24 (±1) after start of menses, with subsequent P concentration of ≥ 16 nmol/L and with next menstruation > 6 days after ovulation
- Body Mass Index ≥ 18 and ≤ 30 kg/m^2
- Good physical and mental health
- Both ovaries visible upon ultrasonography
- Willing to give informed consent in writing

MAIN CRITERIA FOR EXCLUSION

- Clinically significant abnormal results of hematology, biochemistry, urinalysis, or ECG
- Clinically significant abnormalities of the uterus and/or ovaries

NAME OF SPONSOR Estetra SRL	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Estetrol (E4)		
NAME OF ACTIVE INGREDIENT Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol		

- Clinically relevant abnormal cervical cytology ≤ 1 year before study start
- Known or suspected breast cancer or a history of breast cancer
- Known or suspected pregnancy
- Lactation
- Status post-partum or post-abortion ≤ 2 months before study start
- Previous use of depot progestogen preparations in the last 6 months
- Use of sex steroids other than the medication of study
- Contraindications for contraceptive steroids

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION

Estetrol, 10 mg and 20 mg. The 20 mg E4 dose was tested alone and in combination with 150 µg desogestrel or 200 mg P4. The study medication had to be taken orally in the evening at approximately the same time. Subjects were assigned to one of the following groups:

- Group 1 (10 subjects): 10 mg E4
- Group 2 (10 subjects): 20 mg E4
- Group 3 (15 subjects): 20 mg E4 and 150 µg DSG
- Group 4 (15 subjects): 20 mg E4 and 200 mg micronized P4

Subjects treated with E4 alone were treated subsequently with 5 mg of lynestrenol for 14 days to protect the endometrium from any possible proliferative effect induced by the E4 monotherapy.

E4 was supplied as a solution, packed in bottles (10 mg E4: lot no. 07P091; batch no. 07V172; 20 mg E4: lot no. 07P092; batch no. 07V171).

DSG was supplied as 75 µg tablets, packed in blisters (Cerazette®; RVG 22743).

Micronized P4 was supplied as 100 mg capsules, packed in blisters (Progestan®; RVG 11473).
Lynestrenol was supplied as 5 mg tablets, packed in blisters (Orgametril®; RVG 00278).

DURATION OF TREATMENT

Subjects treated with E4 and DSG or with E4 and P4 were treated for 28 days.
Subjects receiving E4 monotherapy were treated for 28 days. If no ovulation took place during the treatment period and a withdrawal bleeding did not start within 3 days after discontinuation of the study medication, these subjects received lynestrenol from 4 days after discontinuation of the study medication for 14 days or until the start of their withdrawal bleeding.

CRITERIA FOR EVALUATION

The present study is designed to investigate the contraceptive effects of E4, alone and in combination with 2 progestogens. Data were collected to evaluate the following variables:

- Follicle development and endometrial thickness were measured by transvaginal ultrasounds
- HPO function was evaluated by measuring of LH, FSH, E2, P, and SHBG
- PK of E4 was investigated by the collection and analysis of plasma samples during the 3 days after the study treatment period
- Safety and tolerability was evaluated by recording hematology, biochemistry, urinalysis, physical, gynecological and breast examinations, blood pressure (BP), heart rate (HR), body weight (BW), and objective and subjective side effects. A questionnaire was completed by the subjects about well-being during study medication use

NAME OF SPONSOR Estetra SRL	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Estetrol (E4)		
NAME OF ACTIVE INGREDIENT Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol		

STATISTICAL METHODS

No formal statistical testing was performed. Analysis of data is based on descriptive statistics.
Efficacy was evaluated by measurements of follicle development, endometrial thickness, laboratory assessments, and the PK analysis of E4.
Safety was evaluated by analysing data collected on hematology, biochemistry, urinalysis, physical, gynecological and breast examination, BP, HR, BW, and objective and subjective side effects.

EFFICACY RESULTS

- Both the ovulation rate and the follicular development according to the Hoogland scoring decreased with increasing dose in the E4-only groups. The combination of 20 mg E4 with P4 or DSG inhibited ovarian function to a greater extent than E4-alone. The contraceptive effect was optimal in the 20 mg E4/DSG group with no ovulations and no follicular development.
- The mean maximum follicle size increased during treatment in the E4-only groups, and to a lesser extent in the 20 mg E4/P4 group. The mean maximum follicle size remained small in the 20 mg E4/DSG group.
- The maximum endometrial thickness increased with increasing dose in the E4-only groups. Both combinations of 20 mg E4 with DSG or P4 did not increase endometrial thickness compared to baseline.
- The LH concentrations decreased compared to the day 3 level in the 20 mg E4/DSG group only. In the other groups the LH concentrations increased compared to the day 3 level. In the E4-only groups LH concentrations increased more than in the 20 mg E4/P4 group.
- The FSH concentrations decreased compared to the day 3 level in the 20 mg E4/DSG group only. The other groups showed a small increase compared to the day 3 level.
- The E2 concentrations decreased compared to the day 3 level in the 20 mg E4/DSG group only. In the E4-only groups E2 increased compared to the day 3 level, the increase being more pronounced in the 10 mg than in the 20 mg E4 group. No conclusions can be drawn for the 20 mg E4/P4 group due to the lack of LC-MS data.
- The P concentrations remained low in the 20 mg E4/DSG group documenting anovulation further. The P levels increased from day 15 onwards in the E4-only groups in subjects who ovulated. Due to the administration of exogenous P4, no conclusions can be drawn for the 20 mg E4/P4 group.
- The SHBG concentrations increased in all treatment groups. SHBG increased dose-dependently in the E4-only groups. The SHBG increase was highest in the 20 mg E4/P4 group and lowest in the 20 mg E4/DSG group.
- A monotherapy of 10 mg or 20 mg E4 did not notably affect the SHBG concentration after the first 2 (±1) treatment days.
- The steady-state E4 levels and the calculated E4 trough levels were highest in the 20 mg E4 dosing group and lowest in the 10 mg E4 dosing group.
- The E4 levels at steady-state and the calculated E4 trough levels varied between the 20 mg treatment groups.
- The mean terminal half life in this study population was 22.25 hours with a large variation. The median terminal half life was 18.10 hours.

SAFETY RESULTS

- The relative number of subjects with at least 1 treatment-emergent adverse event (TE-AE) was comparable in the different treatment groups.
- The mean number of TE-AEs reported per subject was lowest in the 20 mg E4/DSG treatment group and highest in the 20 mg E4/P4 treatment group. The TE-AE incidence was comparable for the E4-only groups.

NAME OF SPONSOR Estetra SRL	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Estetrol (E4)		
NAME OF ACTIVE INGREDIENT Estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol		

- The most frequently reported TE-AEs were in the SOCs of gastrointestinal disorders, infections and infestations, and nervous system disorders. The incidence of these reports was not equally distributed over the treatment groups.
- Severe TE-AEs were reported by 9.6% of the subjects. No severe TE-AEs were reported by subjects treated with E4-only.
- The incidence of drug-related TE-AEs was notably highest in the 20 mg E4/P4 group. The most frequently reported drug-related TE-AEs were PTs dizziness, headache, and abdominal pain lower. Drug-related dizziness was reported in the 20 mg E4/P4 group only. No drug-related headache was reported in the 10 mg E4 group, and no drug-related abdominal pain lower was reported in the 20 mg E4 and 20 mg E4/DSG groups.
- TE-AEs leading to discontinuation were reported for 2 subjects overall (1 subject in the 20 mg E4 group and 1 subject in the 20 mg E4/P4 group). These TE-AEs were single events of regurgation, gastroenteritis, diarrhoea, dizziness, and affect lability.
- One in-treatment pregnancy occurred in the 20 mg E4 group after a confirmed ovulation. The pregnancy was electively aborted.
- No deaths or SAEs occurred during the study.
- No safety concerns were raised from the analysis of hematology and biochemistry parameters.
- The incidence of the abnormal presence of urinary Hb and leukocytes was higher at the end of study treatment in the E4-combination groups. The incidence of bacteria in the urine was higher in the 20 mg E4/DSG group.
- No safety concerns were raised from the analysis of physical examinations, gynaecological examinations, or vital signs.
- Overall, the incidence of improvement of acne compared to baseline was notably higher than the incidence of worsening of acne. Skin improvement was mainly observed in the E4-combination groups.
- Most subjects experienced no change in subjective feelings during study medication use. Reporting of a negative change of subjective feelings was higher in the E4-combination groups than in the E4-only groups.

CONCLUSIONS

In conclusion, E4 dose-dependently inhibits ovarian function up to a dose of 20 mg per day. However, inhibition of ovulation in all subjects was only observed when a progestogen was added. The treatment with 20 mg E4 combined with 150 µg DSG inhibited ovulation adequately and suppressed follicular growth and the HPO axis effectively. In addition, this combination did not increase the endometrial thickness. With 20 mg E4 combined with 150 µg DSG, the increase of SHBG is far less than with OCs containing EE and DSG.

Estetrol was well tolerated and there was no evidence of any safety problem.

DATE OF FINAL REPORT

09FEB2012 (Version 1.0)

DATE OF SYNOPSIS

14JUN2022 (Version 2.0 for Disclosure and Transparency)