A single-center, randomized, open-label, two-arm study to evaluate the ovarian function inhibition of a monophasic combined oral contraceptive (COC) containing 15 mg estetrol (E4) and 3 mg drospirenone (DRSP) and a monophasic COC containing 20 mcg ethinylestradiol (E4)/3 mg drospirenone (Yaz®), administered orally once daily in a 24/4 day regimen for three consecutive cycles

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Primary- To evaluate the effects of the 15 mg E4/3 mg DRSP combination and the 20 mcg EE/3 mg DRSP used as reference combination on ovarian function inhibition at Treatment Cycle 1 and Treatment Cycle 3.Secondary- To evaluate levels of luteinizing...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON43032

Source
ToetsingOnline

Brief title
E4/DRSP Ovarian Function Inhibition Study

Condition

- Other condition

Synonym
birth control, contraception

Health condition

contraception

Research involving
Human

Sponsors and support

Primary sponsor: Estetra SPRL
Source(s) of monetary or material Support: Estetra SPRL

Intervention

Keyword: combined oral contraceptive, ovarian function inhibition

Outcome measures

Primary outcome

Ovarian suppression as assessed with the Hoogland score at Treatment Cycle 1

and Treatment Cycle 3 based on:

* follicular size assessed by TVUS

* endogenous hormone levels: serum E2, and serum progesterone

In case of suspicion of ovulation, additional progesterone measurement will be

scheduled on Cycle Day 2, 4 and 6 after suspected ovulation

Secondary outcome

* Levels of serum FSH, LH, E2, progesterone on Cycle Day 3, 6, 9, 12, 15, 18,

21, 24, 27 (all days ± 1 day) at Treatment Cycle 1 and Treatment Cycle 3 and on Cycle Day 3 (± 1 day) of Treatment Cycle 2;

* Endometrial thickness;

* Return to fertility will be assessed by monitoring follicular growth using TVUS every 3 days from Cycle Day 3 of the Post-Treatment Cycle until ovulation occurs or until Cycle Day 36 (all days ± 1 day). Ovulation will be confirmed by measurement of serum progesterone 2 days after the suspected ovulation. If serum progesterone is < 16 nmol/L, a second measurement of serum progesterone will be obtained 4 days after the suspected ovulation;

* Safety and tolerability will be assessed by the monitoring of AEs, vital signs, physical and gynecological examination, clinical laboratory (including the cardiac profile parameters LDH1, LDH2 and troponin I and T), 12-lead ECG and echocardiogram.

* The effect of 15 mg E4/3 mg DRSP and 20 mcg EE/3 mg DSRP combination on dysmenorrhea and breast tenderness/pain will be assessed using a scoring scale. The scoring scale will ask the subjects to self-assess their perception on dysmenorrhea symptoms and breast tenderness/pain on a scale of 0 to 10 ranging from no complaints (0) to hurts most (10).

Study description

Background summary

Combined hormonal contraception refers to birth control methods that act on the endocrine system to inhibit ovulation. Traditionally the combined oral contraceptives (COCs) contain 2 steroids: one with progestogenic and the other with estrogenic effects. The function of the progestin is to inhibit ovulation by a central feedback mechanism resulting in decreased luteinizing hormone (LH) secretion by the pituitary gland. The estrogen component also contributes to contraceptive activity by inhibiting the secretion of follicle-stimulating hormone (FSH) but the major function of estrogens included into the contraceptive pill is to provide stability to the endometrium and consequently to provide acceptable cycle control and bleeding pattern. Additionally, it prevents estrogen deficiency (manifested as vaginal atrophy and decreased bone formation). COCs have been shown to be highly effective in terms of contraception. They are widely used in the industrialized world.

Estetra SPRL is developing a new COC containing a synthetic form of a natural estrogen called estetrol (E4) combined with drospirenone (DRSP) as progestin.

E4 is only produced by the human fetal liver. It reaches the maternal circulation through the placenta. E4 has been isolated in maternal urine as early as Week 9 of gestation. At pregnancy term, the hormone is found at relatively high concentration (about 1 ng/mL) in maternal plasma and at over 10 times higher in fetal plasma.

DRSP is an analogue of the aldosterone antagonist, spironolactone, with a pharmacological profile more closely related to that of natural progesterone. It is devoid of androgenic, estrogenic, glucocorticoid, and anti-glucocorticoid activity, but possesses potent anti-mineralocorticoid and anti-androgenic properties. DRSP is a progestogin with established use in COCs in combination with ethinylestradiol (EE) (Yasmin®, Yaz®). The use of EE/DRSP combined tablets, in addition to its contraceptive efficacy, may minimize estrogen-inducing water and sodium retention, and reduce side effects such as breast tension, weight gain and acne, which can occur with conventional COCs combining EE and levonorgestrel (LNG). Yaz® has also been shown to improve symptoms of premenstrual syndrome.

A COC containing 15 mg E4 and 3 mg DRSP administered for 24 days followed by 4 placebo tablets, is being evaluated for further development. This study will investigate the effect of this COC on ovarian function inhibition, hypothalamic pituitary ovarian (HPO) axis suppression during 3 treatment cycles and return to fertility after 3 treatment cycles in comparison with the reference COC 20 mcg EE/3 mg DRSP.

Study objective

Primary
- To evaluate the effects of the 15 mg E4/3 mg DRSP combination and the 20 mcg EE/3 mg DRSP used as reference combination on ovarian function inhibition at Treatment Cycle 1 and Treatment Cycle 3.

Secondary
- To evaluate levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) and progesterone during Treatment Cycle 1, (Treatment Cycle 2), and Treatment Cycle 3.
- To evaluate endometrial thickness.
- To evaluate return to fertility.
- To assess the safety and tolerability of the 15 mg E4/3 mg DRSP and the 20 mcg EE/ 3 mg DRSP combination.

Exploratory
- To evaluate the effect of 15 mg E4/3 mg DRSP and the 20 mcg EE/3 mg DRSP combination on dysmenorrhea and breast tenderness/pain

Study design

This is a single-center, randomized, open-label, controlled, two-arm study in healthy female subjects. Subjects will be stratified according to day of ovulation in the Pre Treatment Cycle and BMI (* 30.0 kg/m2 and > 30.0 kg/m2) to ensure an even distribution over treatment groups. Each subject will undergo a screening visit, a Pre Treatment Cycle, followed by 3 treatment cycles, a Post-Treatment Cycle, and a follow-up visit. In case of use of hormonal contraception at least 1 wash-out cycle has to be performed before start of the Pre-Treatment Cycle.

Subjects will visit the clinic regularly during the Pre-Treatment Cycle, Treatment Cycle 1 and Treatment Cycle 3 and the Post-Treatment Cycle. One visit is planned during Treatment Cycle 2.

Treatments will be administered once daily during 3 treatment cycles of 24 days of active medication followed by 4 days of placebo.

Intervention

The study will start with a screening visit. During the screening visit standard medical assessments including safety laboratory tests (blood draw), a physical examination and a vital signs measurement will be performed. In addition a standard gynecological examination will be performed including a cervical smear (if not done in the past 18 months). The subject will also visit

the UMCG for an ECG and echocardiogram.

After the subject passes all above mentioned tests, the subject will enter the pre-reatment cycle. In the pretreatment cycle vital signs, ovulation and endometrial thickness will be analyzed. In addition the subject will score their levels of dysmenorrhea and breast tenderness/pain.

Following the pre-treatment cycle subjects will be randomized to 1 of the 2 study arms. During cycle 1-3 vital signs, ovulation and endometrial thickness measurements are repeated. In addition the subject will score their levels of dysmenorrhea and breast tenderness/pain. At the end of cycle 3 subjects will visit the cardiologist for an echocardiography and ECG.

After cycle 3 subjects will enter the post treatment cycle. In the post treatment cycle, ovulation and endometrial thickness will be analyzed. In addition the subject will score their levels of dysmenorrhea and breast tenderness/pain.

After the pre, during and follow-up cycles have been completed, the subject will visit the clinic for a final visit.

Subjects will be asked on a regular basrs for possible side effects throughout the study. Cornpliance of the study medication will be monitored by means of a paper diary. This diary will be completed by the subjects each day.

Study burden and risks

The most commonly observed side effects of combined contraceptive pills (the pill) are: nausea, stomach pain, changes in weight, headache, including migraines, mood changes, including depression, breast tenderness or pain, or problems with your periods such as irregular periods, absence of periods.

Drawing blood may be painful or may cause some bruising.

Vaginal ultrasound examinations are usually painless. An ultrasound examination does not pose any risk to you. Inserting the speculum and taking a smear of the cervix can be somewhat discomfortable. You may have some light bleeding afterwards.

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

All inclusion criteria defined in the study protocol (section 3.3.1) must be met for a subject to be eligible for inclusion in the study

Exclusion criteria

A subject who meets any of the exclusion criteria defined in the study protocol (section 3.3.2) will not be eligible for inclusion in the study:

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-02-2017
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	not applicable
Product type:	Medicine
Brand name:	Yaz
Generic name:	Ethinylestradiol / Levonorgestrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	14-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	06-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-004267-40-NL
CCMO	NL60048.056.16