Characterisation of ovulation inhibition and effects on metabolic parameters and haemostatic system of multiple administrations of a fixed-dose combination product containing 0.02 mg ethinylestradiol and 2 mg dienogest (24+4) in a multiple administration, comparative parallel-group trial vs. a marketed product containing 0.02 mg ethinylestradiol and 0.10 mg levonorgestrel with healthy females of childbearing potential

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descriptive characterisation of the influence of Test or Reference on ovarian activity determined by means of maximum follicular diameter and Hoogland scoredescriptive characterisation of the effect of Test or Reference on endometrial thickness,...

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

Summary

ID

NL-OMON37701

Source
ToetsingOnline

Brief title
Ovulation inhibition study

Condition

- Other condition

Synonym
hormonal contraception, inhibition of ovulation

Health condition

inhibition of ovulation

Research involving
Human

Sponsors and support

Primary sponsor: Zentiva k.s.
Source(s) of monetary or material Support: Zentiva / SocraTec R&D

Intervention

Keyword: haemostatic system, inhibition, metabolic parameters, ovulation

Outcome measures

Primary outcome

descriptive characterisation of the influence of Test or Reference on ovarian

activity determined by means of maximum follicular diameter and Hoogland score

Secondary outcome

descriptive characterisation of the effect of Test or Reference on endometrial

thickness, cervical mucus as well as on the pituitary and ovarian hormones the

latter determined via follicle stimulating hormone (FSH), luteinising hormone

(LH), estradiol (E2) and progesterone (P)

descriptive characterisation of effect of Test or Reference on sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) levels, C-reactive protein, lipid profile as well as haemostatic and carbohydrate parameters

descriptive characterisation of bleeding pattern

descriptive characterisation of return of ovulation

descriptive characterisation of overall safety and tolerability in the study population.

Study description

Background summary

The present trend in development of oral contraceptives is to reduce hormonal content especially with regard to the oestrogen component to maintain efficacy and to minimise oestrogen-related side effects. Historically, oral contraceptives with lower doses of ethinylestradiol were sought after because of the cardiovascular risks associated with the use of higher doses of EE [6].

Such an approach has successfully been applied for a combination of 0.02 mg EE with LNG (Microgynon® 20, Miranova®). However, reduction in daily EE dose comes along with a reduced inhibition of ovulation so that an increase in the risk of follicular rupture and ovulation is expected.

As a consequence of these mechanistic and pharmacological considerations, it is the intention to develop a combination product with 0.02 mg EE and 2.0 mg DNG specified for 24 active treatment days and 4 days of treatment-free interval.

Study objective

descriptive characterisation of the influence of Test or Reference on ovarian

activity determined by means of maximum follicular diameter and Hoogland score

descriptive characterisation of the effect of Test or Reference on endometrial thickness, cervical mucus as well as on the pituitary and ovarian hormones the latter determined via follicle stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2) and progesterone (P)

descriptive characterisation of effect of Test or Reference on sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) levels, C-reactive protein, lipid profile as well as haemostatic and carbohydrate parameters

descriptive characterisation of bleeding pattern

descriptive characterisation of return of ovulation

descriptive characterisation of overall safety and tolerability in the study population

Study design

This clinical trial will be performed in a single centre, open-label, randomised (assignment to treatment group), parallel-group, two-arm multiple-dose design.

60 healthy pre-menopausal women aged between 18 and 35 years with proven potential for ovulation are intended to be randomised.
The clinical trial comprises three phases, i.e. pre-treatment phase, treatment phase and follow-up phase.
The pre-treatment phase includes a pre-treatment menstrual cycle for check of subjects* potential for ovulation as well as baseline assessment of SHBG and CBG levels, C-reactive protein, lipid profile, haemostatic and carbohydrate parameters. After subjects have been found eligible for the clinical trial they will be randomised.

Afterwards, subjects will enter the treatment phase and will receive either Test or Reference treatment stratified by time point of ovulation in the pre-treatment cycle. IMPs will be administered as multiple oral doses over three treatment cycles (T1, T2 and T3) of 28 days each. Per treatment cycle, in case of Test 24 tablets containing each 0.02 mg EE and 2 mg DNG will be administered over 24 days followed by a treatment-free interval of 4 days. In case of Reference 21 tablets containing each 0.02 mg EE and 0.1 mg LNG will be administered over 21 days followed by a treatment-free interval of 7 days. Overall, 72 tablets of Test or 63 tablets of Reference will be administered. Ovarian activity will be monitored under treatment. During the treatment cycle 3 changes from baseline of the above mentioned clinical laboratory parameters will be assessed.

Subsequently, subjects will enter the follow-up phase, for monitoring of return of ovulation over one menstrual cycle.

Intervention

n.a.

Study burden and risks

The following side effects have been described for the investigational products.

Common side effects (>= 1/100 and < 1/10) are: headache, abdominal pain, and breast pain.
Uncommon side effects (>= 1/1000 and < 1/100) are: fungal infection of the vagina, increased appetite, depressed mood, migraine, dizziness, nervousness, eye complaints, vein complaints, hypertension, gastrointestinal disturbances, nausea, vomiting, acne, exanthema, eczema, alterations of the skin, chloasma (increased pigmentation), alopecia (loss of hair), cramps in the legs, urinary tract infection, bleeding disturbances, dysmenorrhoea (menstrual pain), breast enlargement, ovarian cyst (benign swelling of ovaries), dyspareunia (disorder of sexual function), vaginitis (inflammation of the vagina), vulvo-vaginitis (inflammation of the outer sexual organs), changes in vaginal secretion, hot flushes, fatigue/weakness, back pain, oedema (swelling).

Rare side effects (>= 1/10.000 and < 1/1000) are: allergic reactions, anorexia (diminished appetite), decreased libido (sexual desire), aggressive reactions, indifference, abnormal vision, conjunctivitis (inflammation of the conjunctiva), deafness, thrombophlebitis (inflammation of veins with blood clot), thrombosis (vascular disease with formation of blood clot)/pulmonary embolism (obstruction of lung artery), tachycardia (increased heart rate), cardiac complaints, haematoma, cerebrovascular (related to blood vessels of brain) disturbances, sinusitis (inflammation of paranasal sinus), asthma, upper respiratory tract infection, diarrhoea (loose bowels), erythema multiforme (inflammatory disease of skin or mucosa), pruritus (itchiness), hypertrichosis (excessive hairiness), virilism (masculinisation), hypomenorrhoea (weak menstruation), mastitis (inflammation of mammary gland), fibrocystic disorders of the breast (changes in breast tissue), breast secretion, leiomyoma (benign tumour of smooth muscle layer), endometritis, (inflammation of uterine lining), salpingitis (inflammation of oviduct), influenza-like symptoms, anaemia (lack of blood).

The following Serious Adverse Reactions have been reported upon use of combined oral contraceptives:
• venous thromboembolic disorders (blood clots in the veins)
• arterial thromboembolic disorders (blood clots in the arteries)
• hypertension

• irregular bleeding
• chloasma (increased pigmentation of skin)
• in women with hereditary angioedema (genetic disease with swelling of skin and various organs) exogenous (applied from the outside) oestrogens may induce or exacerbate symptoms of angioedema
• liver tumours
• cervical carcinoma (tumours of neck of uterus)
The frequency of diagnosis of breast cancer is slightly increased among users of oral contraceptives. As breast cancer is rare in women under 40 years of age, the risk to develop cancer is small in relation to the overall risk.

Furthermore, the following Adverse Events have been reported upon use of combined oral contraceptives; frequency is not calculable based on available reports:
• neuritis nervi optici (partial or total loss of vision possible)
• deterioration of varicose veins (enlarged and tortuous veins)
• pancreatitis (inflammation of pancreas) in case of concurrent hypertriglyceridemia (increase in blood fat values)
• cholecystic diseases including cholelithiasis (crystalline concretion formed within the gallbladder)
• haemolytic-uremic syndrome (disease of small blood vessels)
• herpes gestationis (immune mediated disease during pregnancy)
• otosclerosis (disease of bones of inner ear)
• deterioration of systemic lupus erythematosus (immune mediated disease)
• deterioration of porphyria (metabolic disease)
• deterioration of Sydenham's chorea (neurologic immune mediated disease)
• deterioration of depression
• deterioration of chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis)

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

Healhy female subjects aged 18-35

Exclusion criteria

Clinically significant abnormalities at screening

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):	28-03-2012
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BONADEA PLUS, film-coated tablet
Generic name:	0.02 mg ethinylestradiol / 2 mg dienogest
Product type:	Medicine
Brand name:	Miranova® coated tablets
Generic name:	0.02 mg ethinylestradiol / 0.10 mg levonorgestrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-03-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2012
Application type:	First submission
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	EUCTR2012-000041-12-NL
CCMO	NL40052.056.12