PK/PD trial with different dose regimens of Cyclogest® in comparison to Crinone® and placebo in healthy female subjects

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To investigate the effect of various dose regimens of Cyclogest® on secretory transformation of the endometrium in comparison to Crinone® and placeboTo investigate single and multiple dose pharmacokinetics of Cyclogest®To investigate safety and...

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

Summary

ID

NL-OMON37494

Source
ToetsingOnline

Brief title
ACT-CYC-100-2012-01

Condition

- Other condition
- Sexual function and fertility disorders

Synonym
Infertility, not able to get pregnant

Health condition

Progesteron supplementation (ART)

Research involving
Human

Sponsors and support

Primary sponsor: Actavis Group PTC ehf
Source(s) of monetary or material Support: Actavis

Intervention

Keyword: endometrium, pharmacokinetics, progesterone, various dose regimens

Outcome measures

Primary outcome

Secretory transformation of the endometrium:

It is defined as binary outcome, i.e. the possible outcomes *early secretory*

and *late secretory* will be combined to *adequate response* and the outcomes

proliferative, *bleeding/necrosis of stratum functionale (menstrual)* to

inadequate response.

Secondary outcome

Histological results with outcomes *early secretory*, *late secretory*,

proliferative and *bleeding/necrosis of stratum functionale (menstrual)*

Endometrial thickness, as assessed by transvaginal ultrasonography

Endometrial aspect, as assessed by transvaginal ultrasonography

AUC(0-12h) after single dosing on Day 15 based on serum concentrations of

progesterone

AUC(0-24h) after multiple dosing based on serum concentrations of progesterone

(i.e. starting from pre-dose on Day 24/evening, and covering two applications

in case of bid treatment regimens)

Safety parameters (adverse events, vital signs, safety laboratory).

Study description

Background summary

Cyclogest Pessaries® are currently developed for the indication of progesterone supplementation as part of an Assisted Reproductive Technology ("ART") treatment for infertile couples. Other products have been developed for this indication but in this study Crinone 8% gel will be the active comparator. Clinicians suggest that Crinone® is dosed too low as they observe more bleeding after this treatment than after Cyclogest®. Crinone® (Merck-Serono) claims to have a sustained release profile with the capability of sticking to the vaginal mucosa.

The sponsor intends to develop Cyclogest® for luteal phase support in women having undergone IVF. It has been requested from MHRA in a Scientific Advice meeting to justify a dose and the duration of treatment before performing a non-inferiority trial in patients with this new indication.

The aim of this trial is to gain information about various dose strengths of Cyclogest® and to collect reliable data with special regard to the pharmacodynamic effect on the endometrium that would allow to design a clinical non-inferiority trial with less patients and/or less risk of failure.

Study objective

To investigate the effect of various dose regimens of Cyclogest® on secretory transformation of the endometrium in comparison to Crinone® and placebo

To investigate single and multiple dose pharmacokinetics of Cyclogest®

To investigate safety and tolerability of single and multiple doses of Cyclogest®

Study design

This is a randomized, single-center observer blind trial including two parts, one consisting of a 3-way crossover (Part 1), and the other consisting of 3 study periods with a 2-way crossover performed in periods 1 and 2 followed by a placebo control in period 3 (Part 2).

Part 1 will be a 3-way crossover with multiple dose application over 10 days of 200 mg Cyclogest® bid, 400 mg Cyclogest® bid, and 90 mg Crinone® od.

Part 2 will consist of a 2-way crossover with multiple dose application over 10 days of 100 mg Cyclogest® bid, 100 mg or 200 mg or 400 mg od followed by placebo treatment (2 times daily application). The dose regimens to be administered (100 mg or 200 mg or 400 mg od) will be defined after the PD results were obtained from Part 1 (after 42 subjects completed period 1).

Taking into account replacement of dropouts, it is estimated that approximately 96 subjects will have to be included into the study in order to obtain 84 evaluable subjects. Subjects who drop out before the end of the second treatment epriod will be replaced

Intervention

The study treatment will consist of a screening and synchronization phase (about 1 to 42 days) followed by three periods of study drug administration over 24 days and 4 treatment / pill free days.

During each treatment period, E2 will be taken orally by the subjects for 24 days (Day 1 to Day 24). The study drug (progesterone or placebo) will be administered concomitantly on Day 15 to 24. Then subjects will have a treatment free period of 4 days (Days 25 to 28), followed by a washout phase of at least 17 days of COC intake followed by 4 pill free days. This wash-out cycle can be repeated according to subject*s feasibility of participating in the next treatment period. After completion of the last treatment period, subjects will have a follow-up visit 16 ±2 days after last application of vaginal study drug

Study burden and risks

Cyclogest® pessary, vaginal administration: menstruation may occur earlier than expected, or, more rarely, menstruation may be delayed. As with other vaginal and rectal preparations, some leakage of the pessary base may occur. There is a wide margin of safety with Cyclogest® pessaries but overdose may produce euphoria and dysmenorrhoea.

Crinone® 8% gel, common side effects are: headache, sleepiness, breast tenderness or vaginal irritation/itching/burning. Side effects reported after marketing: intermenstrual bleeding (spotting), hypersensitivity reactions usually manifesting as skin rash, and other mild application site reactions.

Rare events of urticaria and pruritus were noted.

Sleepiness might affect the ability to drive

Baseline treatments

Progynova®, The following undesirable effects have been reported during the use of Progynova® as hormone replacement therapy for peri- and postmenopausal women or for prevention of osteoporosis: hypersensitivity reaction, worsening of hereditary angioedema (skin disease), worsening of porphyria (enzyme disorder), increased or decreased weight, increased appetite, decreased glucose (sugar) tolerance, anxiety/depressive symptoms, decreased or increased libido, migraine, headache, dizziness, fatigue, chorea (nerve disease), stroke, visual disturbances, intolerance to contact lenses, palpitations, myocardial infarction, hypertension, thrombophlebitis (vein infection with blood clots), venous thromboembolism (blood clot in vein or lung artery), nose bleed, dyspepsia (disturbed digestion), abdominal pain, vomiting, nausea, bloating, flatulence, gall bladder disease including gallstones, rashes, various skin disorders (including itching, eczema, urticaria, acne, excessive body hair growth, hair loss, erythema nodosum (skin rash with painful blue-red nodules), erythema multiforme (skin rash, may be associated with nodules, vesicles, or fluid retention), hemorrhagic rash, chloasma (yellow-brown pigment spots, especially in the face), leg pain, cystitis-like symptom, increased size of uterine fibroids, vaginal candidosis, uterine cervical erosions, changes in vaginal bleeding pattern and abnormal bleeding or flow, breakthrough bleeding, spotting, dysmenorrhoea, changes in vaginal secretion, premenstrual-like syndrome, breast secretion, breast tenderness, enlargement or pain, oedema, breast cancer, endometrial cancer.*

Microgynon® 30, Common side effects are: nausea, abdominal pain, weight increase, headache, depressed mood, altered mood, breast pain, breast tenderness. Uncommon side effects are: vomiting, diarrhoea, fluid retention, migraine, decreased libido, breast growth, rash, urticaria. Rare side effects are: contact lens intolerance, hypersensitivity, decreased weight, increased libido, vaginal discharge, breast discharge, erythema nodosum (skin rash with painful blue-red nodules), erythema multiforme (skin rash, may be associated with nodules, vesicles, or fluid retention). Side effects reported after marketing are: worsening of hereditary angioedema (skin disease), hypertriglyceridemia (elevated blood triglyceride (lipid) levels), worsening of chorea (nerve disease), Crohn*s disease, ulcerative colitis (chronic bowel infections), liver function disturbances, reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, absence of bleeding after stopping pill intake, chloasma (yellow-brown pigment spots, especially in the face).

The following serious adverse events have been reported in women using combined oral contraceptives: venous thromboembolic disorders (deep venous thrombosis

and lung embolia which means blood clot in vein or in lung artery), arterial thromboembolic disorders (blood clot in artery), strokes (e.g. TIA (temporary loss of a part of the brain function), ischemic stroke (brain infarction), haemorrhagic stroke (bleeding in the brain)), hypertension, liver tumors (benign and malignant).

The following conditions are reported to deteriorate with pregnancy or previous COC use: jaundice and/or pruritus related to cholestasis; gallstone formation, systemic lupus erythematosus (immune disease); herpes gestationis (herpes during pregnancy); otosclerosis-related hearing loss (ear disease); sickle cell anaemia; renal dysfunction; hereditary angioedema (skin disease); porphyria (enzyme disorder); cervical cancer.

Changes in carbohydrate metabolism have been reported in women using combined oral contraceptives.

Provera®, the following medical events have been occasionally to rarely reported in relation to the use of progestogens like Provera®: hypersensitivity reactions, e.g. anaphylaxis and anaphylactoid reactions (general allergic reactions) and angioedema (swelling), weight change, oedema/fluid retention, depression, sleeplessness, nervousness, dizziness, headache, sleepiness, thromboembolic disorders (blood clot in artery or vein), nausea, acne, alopecia (baldness), hirsutism (excessive body hair growth), itching, rash, urticaria, breast secretion, breast tenderness, breast pain, tiredness, decreased glucose (sugar) tolerance.

General, Generally, side effects of the investigational medication that have been unknown so far must always be expected. If during this study more information becomes available about this study medication, especially when this can affect the readiness to participate, the subjects will be informed.

The frequency of diagnosis of breast cancer is slightly increased among users of oral contraceptives and among women using hormonal preparations after menopause. As breast cancer is rare in women under 40 years of age, the extra risk to develop cancer is small in relation to the overall risk of breast cancer. It is unknown if combined oral contraceptive use can cause breast cancer.

A blood withdrawal or insertion of the cannula for blood sampling might be painful or the subject may become temporarily dizzy. Furthermore, the subject may experience intermittent complaints like re-bleeding or puncture site bruise, blot clot in the punctured vessel (rarely), puncture site infections (rarely) or mechanical nerve damage (very rarely).

Taking a biopsy of the lining of the subjects uterus may be painful during the several seconds the procedure takes. Cramping and lower abdominal pain may occur for minutes to hours afterwards. A painkiller is recommended to be used

before the biopsy to prevent or relieve the pain. The subjecy may experience some light vaginal bleeding for a day or two. Very rarely, the procedure may result in perforation of the uterus or infection which may require hospitalization to treat.

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

Healthy female volunteers aged >=18 and <= 45 years

Exclusion criteria

Clinically significant abnormalities at screening

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-05-2012
Enrollment:	96
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Crinone gel (8%)
Generic name:	Progesterone
Product type:	Medicine
Brand name:	Cyclogest pessary 100 mg
Generic name:	Progesterone
Product type:	Medicine
Brand name:	Cyclogest pessary 200 mg
Generic name:	Progesterone
Product type:	Medicine
Brand name:	Cyclogest pessary 400 mg
Generic name:	Progesterone

Ethics review

Approved WMO Date:	09-05-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-07-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-09-2012
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	EUCTR2012-001726-95-NL
CCMO	NL40500.056.12