A randomized, double-blind, placebo-controlled, parallel, single center study to investigate the pharmacokinetics, safety, and tolerability of Estetrol (E4) in combination with Drospirenone (DSRP) after single and multiple dosing in healthy women.

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

Summary

ID

NL-OMON43025

Source
ToetsingOnline

Brief title
E4/DRSP single and multiple dose PK and early QT study.

Condition

- Other condition

Synonym
Prevention of pregnancy.

Health condition

Zwangerschapspreventie.

Research involving
Human

Sponsors and support

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

Intervention

Keyword: E4/DRSP, Estrogen/progestogen, Prevention of pregnancy

Outcome measures

Primary outcome

To investigate the pharmacokinetics (PK) of single and multiple doses of

estetrol (E4) in combination with drospirenone (DRSP) in healthy women

Secondary outcome

To investigate the safety and tolerability of single and multiple doses of E4

in combination with DRSP in healthy women.

To define the effect of E4 in combination with DRSP on QT interval corrected

with Fridericia*s formula (QTcF) in healthy women using exposure-response

analysis.

To define the effect of E4 in combination with DRSP on heart rate (HR), PR, and

QRS in healthy women.

Study description

Background summary

The combined oral contraceptive pill (COCP), often referred to as the birth control pill or just *the pill*, is a birth control method that includes a combination of two types of hormones: an estrogen (usually ethinyl estradiol) and a progestogen. When taken orally every day, the pill inhibits fertility. Estelle® is being developed by Estetra SPRL as a new COCP containing a new estrogen called *estetrol* (also called *E4*) and an existing progestogen called *drospirenone* (DRSP). E4 is a natural estrogen only produced by the fetal liver during human pregnancy. DRSP is the progestogen used in some marketed COCPs (such as Yaz®). The combination of E4 and DSRP is expected to have the same efficacy as current COCPs but with fewer side effects often seen with COCPs containing ethinyl estradiol. Estelle® is not registered as a drug but has been given to humans before.

Study objective

The purpose of the study is to investigate how quickly and to what extent single and multiple doses of Estelle® are absorbed by and eliminated from the body (this is called pharmacokinetics). It will also be investigated how safe Estelle® is and how well Estelle® is tolerated, amongst others by looking at the effects on the electrical activity of the heart at doses that are higher than the expected optimal dose for contraception, being 15 milligrams (mg) E4 and 3 mg DRSP (see next Chapter *How much of the study compound will I receive?*). Amongst others, it will be evaluated if there is a prolongation of the so-called QT interval; the QT interval is a variable measured by a heart trace. When the QT interval is prolonged, repolarization is delayed. This means that cardiac cells need more time to prepare for the next beat. When a new heartbeat is about to start and not all cardiac cells are prepared for that, arrhythmias (heart rhythm problems) may develop. Safety and tolerability will further be investigated by looking at blood parameters and by making an echocardiogram.
This study will be performed in a maximum of 56 healthy female volunteers divided over 4 groups of 14 volunteers.

Study design

Before the study the volunteers will undergo a pre-study screening within 49 days before the first day of administration of the study compound (Day 1) during which they will be subjected to a number of medical examinations. Similar examinations will be performed after the study at the post-study screening which will be conducted within 36 to 40 days (Day 37-41) after the first day of administration of the study compound. The appointment for the post

study screening will be made with the volunteers during the study.

After the initial pre-study screening, they will undergo a second pre-study screening. During this second pre-study screening, a cervical smear test and a bimanual examination of the uterus will be performed in the Martini Hospital in Groningen. The cervical smear test will not be needed when it has been done within 1 year prior to this screening, when PRA has the permission to request the results from the general practitioner and when the result of the test is available and normal.

The actual study will consist of 2 periods as follows:
* Period 1 starts on Day -2 (2 days before first administration of the study compound) and ends on Day 14:
o On Day -2, they are expected at 8:30 hours in the morning in the clinical research center in Groningen. They will leave in the morning of Day 3; thus they will stay for 5 days (4 nights).
o On Days 4, 5, 6, 7 and 8, they are expected for a short visit at 8:30 hours in the morning in the clinical research center in Groningen; they will leave the clinical research center within a few hours. Subsequently they are not expected anymore in the clinical research center up to Day -14.
* Period 2 starts on Day 15 and ends on Day 35:
o On Days 15, 17, 19, 21, 23 and 25, the volunteers are expected for a short visit at 8:30 hours in the morning in the clinical research center in Groningen; they will leave the clinical research center at the beginning of the afternoon.
o On Day 26, they are expected at 14:00 hours in the afternoon in the clinical research center in Groningen. They will leave in the morning of Day 29; thus they will stay for 4 days (3 nights).
o On Days 30, 31, 32, 33, 34 and 35, the volunteers are expected for a short visit at 8:30 hours in the morning in the clinical research center in Groningen; they will leave the clinical research center within a few hours.

Intervention

Group Dose Level E4 (mg) Dose Level DRSP (mg) Dosage
Group 1 15 3
therapeutic E4/DRSP dose level
Group 2 30 6 2
times therapeutic E4/DRSP dose level
Group 3 60 12 4
times therapeutic E4/DRSP dose level (supratherapeutic dose)
Group 4 TBD TBD
TBD

Study burden and risks

Pain, minor bleeding, bruising, possibly an infection due too blood sampling.

Contacts

Public
Estetra SPRL

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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 subjects
18-50 years, inclusive
BMI 18.0-35.0 kg/m2, inclusive
non-smokers

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-04-2016
Enrollment:	56
Type:	Actual

Ethics review

Approved WMO Date:	30-03-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	19-05-2016
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	EUCTR2016-000861-22-NL
CCMO	NL57271.056.16