A Phase 1, randomized, open-label, active comparator- and no-treatment controlled, parallel-group, clinical trial to assess the effects on metabolic parameters of MK-8342B (etonogestrel + 17ß-estradiol [ENG-E2] vaginal ring) compared with the levonorgestrel 150 µg + ethinyl estradiol 30 µg (LNG-EE) combined oral contraceptive (COC) and no-treatment control in healthy adult women.

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The primary objective of this study is:After 3 treatment cycles in healthy female subjects between the ages of 18 and 50 years (inclusive): To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC on hemostatic parameters that...

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

Summary

ID

NL-OMON43381

Source
ToetsingOnline

Brief title
A study to assess the effects of MK-8342B on metabolic parameters

Condition

- Other condition

Synonym
birthcontrol, contraception

Health condition

anticonceptie

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: bedrijf

Intervention

Keyword: LNG-EE combine oral contraceptive, vaginal ring

Outcome measures

Primary outcome

The EMA requires that all new combined hormonal contraception (CHC) products assess the impact of treatment on hemostatic parameters by providing comparative pharmacodynamic data of the new CHC to a marketed EE-and levonorgestrel- or desogestrel-containing COC, with an established risk profile [3]. The EMA acknowledges that there are no generally accepted surrogate endpoints for rare risks associated with CHCs, such as cardiovascular events or VTE. The Guideline on Clinical Investigation of Steroid Contraceptives in Women (July 2005) [3], suggests that the biologic variables that may reflect pharmacodynamic alterations, possibly related to VTE risk, may include, prothrombin fragment 1+2, APC resistance (ETP-based and APTT-based), d-dimer,

factor VII, factor VIII, factor II, antithrombin, protein S, protein C, and SHBG. For the current study, a subset of hemostatic parameters, those previously shown to be differentially altered by COCs containing EE or E2 based on published reports [1, 2, 11], were selected as the primary study endpoint. The hemostatic parameters selected to support the primary study objective include Tissue Factor Pathway Inhibitor antigen (TFPI), protein S antigen (total), antithrombin activity, d-dimer, and normalized Activated Protein C resistance ratio (nAPCrr). A combination of hemostatic parameters was selected considering that no individual hemostatic parameter has been established as the single-most predictor of VTE risk.

The proposed duration for assessment of hemostatic parameters is after three cycles of treatment with the ENG-E2 vaginal ring. The change from baseline to end of Cycle 3 for each parameter will be determined and an estimate of the treatment differences provided, along with the 95% confidence interval (CI). Three months is considered to be a sufficient duration of time to detect hormonal effects on the specified hemostatic parameters. In the study by Agren et al., hemostatic parameters measured after 3 months and 6 months of treatment were similar, indicating that the additional 3-month time period was not needed to allow hormonal effects to become manifested. Additionally, in a study by Johnson et al. (2008), assessments were performed after 2 months of treatment and showed that this duration was sufficient to detect treatment differences for hormone-sensitive hemostatic parameters [4].

Secondary outcome

A secondary objective of this study is to assess the effects of the ENG-E2

vaginal ring on additional hemostatic parameters, to ensure that a comprehensive characterization with respect to coagulation is provided, including those cited by the EMA for consideration in the evaluation of new CHCs. The additional hemostatic parameters include: prothrombin fragment 1+2, Protein S (free), APTT-based APCrr, Factor VII, Factor VIII, Factor II, and protein C. Similar to the primary objective, the change from baseline for each parameter after 3 months of treatment with the ENG-E2 vaginal ring will be compared with LNG-EE oral tablets.

An additional secondary endpoint will include CRP and SHBG. C-reactive protein (CRP), a biomarker of inflammation and is considered to be an independent cardiovascular risk marker. CRP has been shown to become elevated after treatment with CHCs [1, 4]. Sex hormone binding globulin (SHBG) has been characterized as a *biomarker* of estrogen-related induction of hepatic protein synthesis, which includes procoagulant hemostatic parameters. In fact, the net SHBG change associated with a CHC depends on the estrogenic-androgenic balance, i.e., the extent to which the estrogen-induced increase is counteracted by the androgenic properties of the progestagen. The change from baseline for each parameter after 3 months of treatment with the ENG-E2 vaginal ring will be compared with the LNG-EE COC.

In addition to assessing impact on hemostatic parameters relative to a CHC (LNG-EE), this study will evaluate whether there is any detectable alteration in hemostatic parameters relative to a non-treated control group. To accomplish this, the change from baseline during ENG-E2 treatment on all of the hemostatic parameters included as the primary or secondary objective will be compared with

changes from baseline in these hemostatic factors in untreated women.
Considering that E2 the concentration-time profile after vaginal administration of E2 is qualitatively and quantitatively similar to naturally occurring menstrual cycles and that there is potentially less induction of hepatic protein synthesis, demonstration of a neutral effect of the ENG-E2 vaginal ring on hemostatic parameters in the current study is expected.
In order to support the ability of this study to assess a neutral effect of treatment with ENG-E2 on hemostatic parameters, the effects of the LNG-EE COC on hemostatic parameters also will be compared with the no-treatment control group, so as to assure assay sensitivity with regard to the comparison of ENG-E2 relative to control and relative to LNG-EE.
The EMA also recommends assessment of the effects of new CHCs on endocrine systems, and suggests measurement of adrenal and thyroid function. In the current study, adrenal function will be assessed by measuring total cortisol and CBG concentrations, and thyroid function by measuring TSH, total and free T4 and TBG concentrations. The change from baseline after three months of treatment with the ENG-E2 vaginal ring will be compared with the LNG-EE COC and the no-treatment control group for these parameters.
The EMA also recommends assessment of the effects of new CHCs on lipid parameters. Fasting lipid parameters include total cholesterol, HDL-cholesterol, non-HDL-cholesterol, apolipoprotein B and triglycerides. These parameters have been shown to be associated with an increase in coronary heart disease (CHD) and modification of these parameters with anti-hyperlipidemic medications, such as statins, reduces risk for CHD and associated outcomes

(e.g., myocardial infarction and stroke) [6]. The change from baseline after three months of treatment with the ENG-E2 vaginal ring will be compared with the LNG-EE COC and the no-treatment control group for these parameters.
The EMA also recommends assessment of the effects of new CHCs on carbohydrate metabolism. Fasting glucose and insulin, glucose and insulin AUC0-2hr after a 75g oral glucose load and HbA1C will be used as glycemic measures to detect alterations in carbohydrate metabolism in this study. As with other assessments, the change from baseline after three months of treatment with the ENG-E2 vaginal ring will be compared with the LNG-EE COC and the no-treatment control group for these parameters.

Study description

Background summary

The EMA requires an assessment of the metabolic profile (hemostatic and lipid parameters, thyroid and adrenal function, carbohydrate metabolism and androgen hormones) to be performed for all new CHC products. For hemostatic parameters, an assessment is provided by comparing the effects of the new CHC to a marketed EE-and levonorgestrel- or desogestrel-containing COC, with an established risk profile. Hence, the proposed study is being conducted to assess the effects of the ENG-E2 vaginal ring on metabolic parameters by determining the treatment difference for change from baseline after 3 treatment cycles with the ENG-E2 125µg/300 µg vaginal ring or LNG-EE 150 µg/30 µg COC

Study objective

The primary objective of this study is:

After 3 treatment cycles in healthy female subjects between the ages of 18 and 50 years (inclusive):

To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC on hemostatic parameters that are differentially modulated by combined oral contraceptives containing EE or E2, including tissue factor pathway inhibitor

antigen (TFPI), protein S antigen (total), antithrombin activity, d-dimer, and normalized endogenous thrombin potential (ETP)-based activated protein C (APC) resistance ratio (nAPCrr).

The secondary objectives of this study are:

After 3 treatment cycles in healthy female subjects between the ages of 18 and 50 years (inclusive):

(1) To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC on hemostatic parameters, including prothrombin fragment 1+2, protein S antigen (free), activated partial thromboplastin time (APTT)-based APCrr, Factor VII activity, Factor VIII activity, Factor II activity, and protein C activity.
(2) To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC on biomarkers of inflammation (C-reactive protein [CRP]) and estrogen-related induction of hepatic protein synthesis (sex hormone binding globulin [SHBG]).
(3) To estimate the effect of the ENG-E2 vaginal ring compared with no-treatment (i.e., control group) on hemostatic parameters including TFPI antigen, protein S antigen (free and total), antithrombin activity, d-dimer, prothrombin fragment 1+2, ETP-based nAPCrr, APTT-based APCrr, Factor VII activity, Factor VIII activity, Factor II activity, protein C activity and hormone-sensitive biomarkers including CRP and SHBG.
(4) To estimate the effect of the LNG-EE COC on parameters of hemostasis compared with no-treatment (i.e., control group) including TFPI antigen, protein S antigen (free and total), antithrombin activity, d-dimer, prothrombin fragment 1+2, ETP-based nAPCrr, APTT-based APCrr, fibrinogen, Factor VII activity, Factor VIII activity, Factor II activity, protein C activity and hormone-sensitive biomarkers including CRP and SHBG.
(5) To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC and no-treatment (i.e., control group) on total cholesterol, high-density lipoprotein (HDL)-cholesterol, non-HDL cholesterol, apolipoprotein B and total triglyceride concentrations.
(6) To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC and no-treatment (i.e., control group) on adrenal function (based on total cortisol and corticosteroid binding globulin [CBG] concentrations) and thyroid function (based on thyroid stimulating hormone [TSH], total and free thyroxine (T4) and thyroid binding globulin [TBG] concentrations).
(7) To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC and no-treatment (i.e., control group) on carbohydrate metabolism, as measured by: fasting glucose and insulin concentrations; glycosylated hemoglobin [HbA1C]; glucose and insulin area under-the-curve from 0 to 2 hours (AUC0-2hr) after an oral 75 g glucose load in healthy women.
(8) To estimate the effect of the ENG-E2 vaginal ring compared with the LNG-EE COC and no-treatment (i.e., control group) on androgenic hormones, including free and total testosterone, dehydroepiandrosterone sulphate (DHEAS), and

androstenedione.
(9) To assess the safety and tolerability of the ENG-E2 vaginal ring after 3 treatment cycles.

Study design

This is a randomized, open-label, active comparator- and no-treatment-controlled, parallel-group, multi-center trial to evaluate the effects of MK-8342B, the etonogestrel (ENG) 125*g/day + 17*-estradiol (E2) 300 *g/day vaginal ring (hereafter referred to as ENG-E2 vaginal ring), on hemostatic and lipid parameters, adrenal and thyroid function, carbohydrate metabolism and androgen hormones

Intervention

Each treatment cycle will be approximately 28-days.
* ENG-E2 vaginal ring group: 21 days with the ENG-E2 vaginal ring inserted, followed by seven (7) days ring-free.
* LNG-EE tablet group: 21 days of LNG-EE oral tablets, taken once daily, followed by seven (7) days of no tablet intake.
* No-treatment Control Group: Untreated for 3 consecutive naturally occurring menstrual cycles.

Study burden and risks

Subject will visit the research doctor 5 times. With the exception of visit 3, blood will be collected during all visits.

the subject may experience physical and / or psychological discomfort experienced by actions performed during the visits, such as gynecological examinations, breast examinations or making a smear.

The subject is asked to keep a diary. This should be recorded every day.

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

VISIT 1:;- Provide written informed consent for the trial. ;- Be a premenopausal female, aged * 18 to *50 years at the time of enrollment.;- If heterosexually active, agrees to have male partner use a condom during the trial period as applicable, unless the subject or her partner is surgically sterilized;- Have a body mass index (BMI) *18 and *35 kg/m2.;- Be in good physical and mental health.;- Be able and willing (in the opinion of the investigator) to adhere to study treatments and to all required study procedures, including study visits.;VISIT 2:;- Have had at least 1 menstruation since Visit 1. ;VISIT 3:;- Have a negative urine pregnancy test at Visit 3.;- Continue to meet all inclusion criteria.

Exclusion criteria

- Is currently smoking or uses tobacco/nicotine containing products and is * 35 years of age.;- Has a history of venous thromboembolic (VTE) events (deep vein thrombosis, pulmonary embolism) or a history of arterial thrombotic or thromboembolic (ATE) events (myocardial infarction, stroke, or peripheral arterial events), or a history of transient ischemic attack, angina pectoris, claudication, or pulmonary hypertension.;- Is at higher risk of VTE events due to recent prolonged immobilization within 2 weeks prior to screening or has a hereditary or acquired predisposition or elevated risk for venous or arterial thrombosis;- Is <35 years of age and has a history of migraine with aura or focal neurological symptoms; or is *35 years of age and has a history of migraines (with or without aura or focal neurologic symptoms);- Has a history of severe dyslipoproteinemia;- Has diabetes mellitus or known insulin insensitivity;- Has clinically significant liver disease;- Has thyroid, adrenal or androgenic disorder (e.g., polycystic ovary syndrome, congenital adrenal hyperplasia, Cushing*s disease or syndrome,

etc).;- Has received any treatment listed in protocol Table 1 more recently than the washout period indicated in Table 1 and/or needs to continue to receive any treatment listed in during the current trial.;NOTE: Refer to protocol for complete list

Study design

Design

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):	25-04-2016
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Microgynon-21
Generic name:	Ethinylestradiol
Registration:	Yes - NL intended use

Ethics review

Approved WMO

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

Approved WMO Date:	25-04-2016
Application type:	First submission
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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	EUCTR2014-003944-11-NL
CCMO	NL56471.056.16