A Phase I, Open-Label Study to Investigate the Pharmacodynamics and Pharmacokinetics of Etonogestrel (ENG) and 17*-Estradiol (E2) in Healthy Young Adult Women Following Administration of MK-8342B (ENG-E2, 125/300 *g/day) Vaginal Ring for an Extended Period of Time

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PrimaryObjective 1: To evaluate the effects of ENG and E2 on ovarian function (pharmacodynamics) when the ENG-E2 vaginal ring (MK-8342B) is used for an extended period of time (i.e., 35 days) in healthy young adult female subjects.Objective 2: To…

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

Summary

ID

NL-OMON43028

Source
ToetsingOnline

Brief title
MK-8342B

Condition

- Other condition

Synonym
contraception, dysmenorrhea

Health condition

hormonal contraception and primary dysmenorrhea in women

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme Corp.;a subsidiary of Merck & Co.;Inc.

Intervention

Keyword: extended period, pharmacodynamics, pharmacokinetics, vaginal ring

Outcome measures

Primary outcome

Pharmacodynamics

The largest follicular diameter, endometrial thickness, and serum

concentrations of P and SHBG will be measured at various time points. Summary

statistics will be provided by time point and Max P and Max FD for the period

will be determined.

Pharmacokinetics

The following pharmacokinetic parameters will be calculated for ENG, E2, and E1

in serum, as appropriate: AUC1-22, AUC1-36, AUC1-44, AUC36-44, Cmin, Cmax,

Tmax, and apparent terminal t*. When multiple time points occur on the same

day, AUC (indicated in study days) are converted into study hours as follows:

* Day 1, Hour 0 is the time of ENG-E2 vaginal ring insertion

* Day 36, Hour 840 is 840 hours post ENG-E2 vaginal ring insertion and the time

of ring removal

Safety:

Safety endpoints will include adverse events, physical examinations,

gynecological examination, vital signs (heart rate and blood pressure), and

clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Secondary outcome

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Study description

Background summary

Therapeutic effect of combined oral contraceptives is based on the hormonal activity of a progestogen and an estrogen. Contraceptives that employ the oral route of administration have a disadvantage in that the drug substance passes through the gastrointestinal tract, possibly resulting in diminished uptake of drug due to interactions with food, degradation, diarrhea, and/or vomiting. In addition, the drug substance will be subject to hepatic first-pass metabolism, requiring a higher dose to achieve the intended effect. This increased daily intake of hormones results in daily peak concentrations that may potentially result in unwanted side effects. Vaginal administration of progestogen/estrogen combinations, as compared to oral administration, is expected to result in more efficient drug delivery (high absolute bioavailability), a controlled release steady pharmacokinetic profile (i.e., absence of daily peaks and troughs), as well as a pharmacodynamic (including metabolic) profile that more closely resembles the physiological state in a fertile female. Vaginal administration is therefore considered a feasible and attractive hormonal contraceptive option.

MK-8342B is a vaginal ring containing a progestogen, ENG, and the estrogen estradiol, E2, referred to in this protocol as ENG-E2. The ring is placed in the vagina and remains in place for 21 days, followed by a 7-day ring-free

interval. During use, the ENG-E2 vaginal ring continuously releases ENG and E2. The vaginal delivery system is made of an ethylene vinylacetate copolymer, similar to the marketed contraceptive vaginal ring NuvaRing®, which contains ENG in combination with ethinylestradiol (EE). ENG-E2 is being developed for contraception and treatment of primary dysmenorrhea.

Study objective

Primary

Objective 1: To evaluate the effects of ENG and E2 on ovarian function (pharmacodynamics) when the ENG-E2 vaginal ring (MK-8342B) is used for an extended period of time (i.e., 35 days) in healthy young adult female subjects.

Objective 2: To characterize the pharmacokinetics of ENG and E2 when the ENG-E2 vaginal ring (MK-8342B) is used for an extended period of time (i.e., 35 days) in healthy young adult female subjects.

Estimation: The effects of extended use (i.e., 35 days) of the ENG-E2 vaginal ring (MK-8342B) on ovarian function and pharmacokinetics of ENG and E2 in healthy young adult female subjects will be estimated.

Secondary

Objective 1: To assess the safety and tolerability of the ENG-E2 vaginal ring (MK-8342B) when used for an extended period of time (i.e., 35 days) in healthy young adult female subjects.

Objective 2: To determine when ovulation occurs post-treatment (i.e., return to ovulation) after the ENG-E2 vaginal ring (MK-8342B) has been used for an extended period of time (i.e., 35 days) in healthy young adult female subjects.

Planned exploratory applicator use

Objective: To obtain further clinical experience with the use of the applicator for placement of the ENG-E2 vaginal ring (MK-8342B) in healthy young adult female subjects.

Planned exploratory biomarker

Objective: To explore the relationship between genetic variation and response to the treatment administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

Study design

This is an open-label, single-center study in young adult female subjects to evaluate the pharmacodynamics and pharmacokinetics of the ENG-E2 vaginal ring. Twenty (20), healthy, adult, female subjects between 18 and 35 years of age (inclusive) will be dosed. To meet this sample size target, approximately 30 subjects will enter the pre-treatment screening period.

Screening of subjects will occur within 10 weeks prior to start of the study treatment period (ENG-E2 vaginal ring insertion). As part of the screening procedures, all potential subjects will be evaluated using vaginal ultrasound scans and P measurement to establish that they have the ability to ovulate. Prior to the start of the pre-treatment screening period, all forms of hormonal contraception will be withdrawn. All subjects must agree not to use hormonal contraception (other than the study drug) through the duration of the study.

On Day 1 of the study, subjects will receive a single ENG-E2 vaginal ring which will be used for an extended treatment period of 35 days. Pharmacodynamic and pharmacokinetic assessments will be obtained throughout the ENG-E2 vaginal ring treatment period until Day 44 post ENG-E2 vaginal ring insertion (i.e., 8 days after ring removal). Subjects who completed the 35-day ring use period will be followed to ensure return of ovulation via
vaginal ultrasound scan and P measurement until confirmed ovulation or until Day 71 (± 1 day) post ENG-E2 vaginal ring insertion (i.e., 35 days after ring removal), whichever occurs first.

Subjects who have started the ENG-E2 vaginal ring treatment but discontinued prior to ENG-E2 vaginal ring removal (Day 36) will not be followed for return of ovulation. Subjects who have started the ENG-E2 vaginal ring treatment but discontinued the study for any reason will be asked to return to the study site for end-of-study procedures approximately 14 days after ENG-E2 vaginal ring removal and to determine if any adverse events have occurred since the last visit. Safety and tolerability will be assessed prior to, during, and following the treatment period with ENG-E2 vaginal ring.

Subjects may be replaced at the discretion of the Sponsor.

Intervention

The Study Events Flow Chart (Section 6 of the protocol) summarizes the clinical procedures to be performed at each visit. I. Additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to subject safety.

For this study, Max FD, endometrial thickness, and blood collection for P, SHBG, ENG, E2, and E1 are the critical parameters. Blood samples need to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

Study burden and risks

The ENG-E2 (125/300 *g/day) vaginal ring administered in this study is not anticipated to induce any potential risk, other than the adverse events associated with the use of hormonal contraceptives, as it is a dose formulation found to be well tolerated in Phase 1 and Phase 2B studies. There will be no direct health benefit for study participants from receipt of the ENG-E2 vaginal ring. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

Details about specific benefits and risks of the ENG-E2 vaginal ring and applicator may be found in the accompanying IB and informed consent documents.

The safety monitoring practices employed by this protocol (i.e., vital signs, clinical laboratory tests, adverse event questioning, gynecological examination, and physical examination) are adequate to protect the subjects* safety and should detect all expected treatment-emergent adverse events.

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

1. Healthy adult female subjects, 18-35 years of age, inclusive, at screening.
2. Continuous non-smokers who have not used nicotine-containing products for at least 3 months prior to ENG-E2 vaginal ring insertion.
3. Body mass index (BMI) * 18.5 and * 30.0 kg/m2, at screening and prior to ENG-E2 vaginal ring insertion.
4. Has good visibility of both ovaries upon ultrasonography at screening.
5. Subjects not using hormonal contraceptives should have regular menstrual cycles ranging from * 21 to * 35 days in length in the 3 months prior to screening.
6. Has ability to ovulate as determined by vaginal ultrasound scan measurements (i.e., measurement of Max FD and double-layer endometrial thickness) during the pre-treatment screening period. Vaginal ultrasound scan measurements will be performed 9 days (± 1) after the start of the last menstruation or withdrawal bleeding and every 3 days ± 1 day onwards until ovulation is observed, during the pre-treatment screening period. After ovulation, the subject must have P levels > 16 nmol/L on two subsequent occasions within 5 days (time of ovulation determined by vaginal ultrasound scan measurement).
7. Medically healthy with no clinically significant abnormalities in medical history, physical and gynecological examination, laboratory profiles, or vital signs, as judged by the Investigator.
8. If sexually active, subject should use a non-hormonal IUD or if she or her partner is not surgically sterilized, agrees to have her male partner use a male condom without spermicide from the time of screening and throughout completion of the study (including the follow-up period).
9. A normal cervical Pap (Papanicolaou) test (Pap <3) within 24 months of screening (first visit) should be documented at the time of screening (first visit); subjects who do not have documentation of normal cervical Pap test within 24 months of screening (first visit) must have a cervical Pap test performed at screening with a normal result. 10. Subject must understand the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol and provides written informed consent for the trial, including for Future Biomedical Research.

Exclusion criteria

1. Subject is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease in

the opinion of the Investigator.
3. History of any illness that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to screening.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. History or presence of: Venous thromboembolic events (VTE), arterial thromboembolic events (ATE), and other major adverse cardiovascular events (MACE) (e.g., myocardial infarction, cerebral vascular accident); headaches with focal neurological symptoms or migraine headaches with aura; breast cancer or undiagnosed breast nodules; hypertension; transient ischemic attacks; liver tumors or liver disease; jaundice with previous use of oral contraceptives or past pregnancy; diabetes; pancreatitis or severe hypertriglyceridemia; carcinoma of the endometrium or other known or suspected estrogen or progestogen dependent neoplasia; cervical cancer.
7. Positive pregnancy test or lactating.
8. Abnormal cervical Pap test within 24 months prior to screening (first visit).
9. Within the past 6 months prior to screening, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the study (e.g., bleeding from cervical polyp, bleeding after sex).
10. Has stage 4 pelvic organ prolapse (1 cm beyond introitus) or lesser degrees of prolapsed with a history of difficulty retaining tampons, vaginal rings, or other products within the vagina.
11. Clinically significant abnormalities of the genital organs as determined by gynecological examination and based on the Investigator*s judgment.
12. Has gonorrhea, chlamydia, or trichomonas or symptomatic vaginitis/cervicitis. Subjects may be rescreened 3 weeks after completing treatment for these conditions.
13. Positive results for the urine drug and/or alcohol breathalyzer screen at screening or on Day 1.
14. Drink alcohol in excess of 14 units per week, with one unit = 125 mL of wine or 284 mL of beer or 25 mL of 45% alcohol.
15. Positive urine cotinine at screening and Day 1 (threshold >100 ng/mL). Note: subjects may be retested if positive.
16. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
17. Unable to refrain from or anticipates the use of any treatment listed in Table 1 of the protocol
18. Hemoglobin level below 11 g/dL at screening.
19. Blood or plasma donation (* 500 mL) within 60 days prior to screening.
20. Donation of bone marrow within the last 6 months prior to screening.
21. Is working at or has an immediate family member (spouse or children) who works at the investigational site or is a Sponsor staff member directly involved with this trial.
22. Participation in another clinical trial within 30 days prior to screening. The 30-day window will be derived from the date of the last blood collection or last dosing, whichever is later, in the previous study to the screening visit of the current study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-06-2016
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	23-05-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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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	EUCTR2016-000693-38-NL
CCMO	NL57712.056.16