A Phase 3, randomized, active-comparator controlled clinical trial to study the contraceptive efficacy and safety of the MK-8342B (etonogestrel + 17*-estradiol) vaginal ring and the levonorgestrel-ethinylestradiol (LNG-EE) 150/30 µg combined oral contraceptive (COC) in healthy women 18 years of age and older, at risk for pregnancy.

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assess the contraceptive efficacy and safety of the etonogestrel (ENG) 125 + 17*-estradiol (E2) 300 µg /day vaginal ring

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

Summary

ID

NL-OMON42732

Source
ToetsingOnline

Brief title
Assessment of contraceptive efficacy & safety of MK-8342B vaginal ring

Condition

- Other condition

Synonym
birthcontrol, contracepetion

Health condition

anticonceptie

Research involving
Human

Sponsors and support

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

Intervention

Keyword: contraceptive, pregnancy, vaginal ring

Outcome measures

Primary outcome

The Pearl Index (PI) was selected as the primary endpoint because it is the standard endpoint used in clinical trials for reporting the effectiveness of contraceptive methods and is widely accepted by regulatory agencies.

The primary efficacy endpoint is the in-treatment pregnancy rate in subjects randomized to the ENG-E2 vaginal ring, between 18 and 35 years of age (at time of enrollment) using the PI, i.e., the number of in-treatment pregnancies per 100 woman-years of at risk exposure. The primary endpoint will be calculated using the rFAS including *at risk* cycles. For the purpose of analysis, *at risk* exposure is defined as cycles in which the subject did not use an additional contraceptive method (other than the trial medication). An in-treatment pregnancy is defined in Section 8.2.12.1. The specified age group, 18-35 years (inclusive) is the standard for PI calculations such that efficacy

is assessed in the age ranges most at risk for pregnancy.

Secondary outcome

Contraceptive efficacy:

The following additional analyses of the PI will be conducted (See Section 3.0):

* Calculation of the PI in women *18 years old using the rFAS

* Calculation of the PI in women ages 18-35 using the PP population (as defined in Section 8.2.3) to demonstrate the *perfect-use* failure rate of the method when used correctly.

* Calculation of PI in women ages 18-35 using the FAS (as defined in Section 8.2.3) to reflect the *typical use* failure rate and more closely represent expected efficacy for real-world use.

* Calculation of the PI in women between 18 and 35 years of age in cycles without use of additional contraception but with the additional requirement for affirmed vaginal intercourse.

Note: This secondary efficacy analysis, requiring affirmed intercourse in addition to no use of additional contraception, will facilitate the cross-trial comparison of contraceptive efficacy of the ENG-E2 vaginal ring to results from a similar trial being conducted in the United States (US), MK-8342B-061, which will assess the PI using this approach.

Cycle Control Analysis (CCA):

A Cycle Control Analysis (CCA) will be performed to determine the bleeding profile for the ENG-E2 vaginal ring and LNG-EE COC. As discussed in Section 8.2.3.1 and 8.2.5.1.2, the primary population for the CCA is the FAS evaluable population which excludes cycles shorter than 22 days or exceeding 35 days or

with 3 or more consecutive days with missing information on bleeding.

The secondary efficacy endpoints to be analyzed in a CCA are parameters

associated with the vaginal bleeding pattern:

* Incidence of BTB-S per cycle [i.e., any bleeding/spotting episode that

occurred during the ring-use/tablet-use interval that is neither an early nor a

continued withdrawal bleeding (WB)]

* Incidence of AWB per treatment cycle (i.e., no bleeding/spotting episode that

began during or continued into the ring-free/tablet-free interval)

Note: BTB-S will not be analyzed for the first treatment cycle due to possible

carryover effects from pre-treatment contraception.

Study description

Background summary

Contraceptive vaginal rings were first described over three decades ago. Administering steroids via the vagina has specific advantages over oral administration including avoiding gastrointestinal absorption and hepatic first-pass metabolism, and providing constant steroid release over a determined time interval avoiding daily fluctuations in medication levels. Early vaginal rings were formulated to release progestagens only. However, due to high levels of irregular bleeding, combined hormonal contraceptive (CHC) vaginal rings were developed to release a progestagen and estrogen.
NuvaRing®, the only combined contraceptive vaginal ring currently marketed, releases 120 µg of the progestagen ENG and 15 µg of the synthetic estrogen EE per day. The design and manufacturing of the ENG-E2 vaginal ring is based on NuvaRing technology with both rings utilizing an ethylene vinyl acetate (EVA) copolymer. Like NuvaRing, the ENG-E2 vaginal ring is easy for a woman to insert and remove. Both rings are inserted at the beginning of a menstrual cycle and remain in the vagina for 21 days. They are intended to be removed on Day 22 of the treatment cycle, the first day of a 7-day ring-free interval.
Unlike oral contraceptives, the monthly contraceptive vaginal ring does not require daily dosing and thus may improve compliance. Experience with NuvaRing suggests that a vaginal ring is acceptable to women. Given the similarities between the ENG-E2 vaginal ring and NuvaRing, comparable acceptability is

expected.
The major difference between NuvaRing and the ENG-E2 vaginal ring is the change in the estrogen component from EE to 17*-estradiol (E2). The use of combined hormonal contraceptives (CHCs) containing EE is associated with an increased risk of venous thromboembolism (VTE) and changes in hemostatic parameters. Recently, E2 has been successfully developed for use in combined oral contraceptives. E2 is identical to the endogenous estrogen produced by the ovaries of fertile women during a normal menstrual cycle. E2-based contraceptives have been shown to have minimal influence on parameters of hemostasis, lipoprotein metabolism, carbohydrate metabolism and acute phase reactants [1, 2]. However, the specific hemostatic (or other) measure(s) that predict risk of VTE with oral CHCs is not established; hence, it is not known whether the use of E2-containing CHCs will have a lower risk of VTE relative to EE-containing CHCs. Based upon the results of a Phase 2b trial (P012), with ENG-E2 vaginal rings releasing 300 µg per day of E2 and various doses of ENG, the pattern of E2 concentrations noted over the treatment cycle resembles physiologic levels of the normal menstrual cycle without the daily peaks and troughs occurring during oral administration. Additionally, in contrast to EE-containing CHCs, ENG-E2 releasing rings did not induce sex hormone binding globulin (SHBG) synthesis, which may reflect limited impact on hepatic protein synthesis. Since the exact mechanism(s) of CHC-induced increased risk of VTE is not determined, it is unknown whether the differences between the ENG-E2 vaginal ring and the EE-containing CHCs will lead to an improved safety profile for the ENG-E2 vaginal ring.

Study objective

assess the contraceptive efficacy and safety of the etonogestrel (ENG) 125 + 17*-estradiol (E2) 300 µg /day vaginal ring

Study design

randomized, active-controlled, parallel-group, multi-center, open-label trial

Intervention

One group uses the ENG-E2 vaginal ring once monthly. The other group will receive LNG-EE 150/30 µg combined oral contraceptive

Study burden and risks

Subject will visit the research doctor at least seven times and maximum 13 times. During all visits blood is collected.

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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Scientific
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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. Provide written informed consent for both the trial and for Future Biomedical Research
2. Be a premenopausal female >18 years old at enrollment
3. Be at risk for pregnancy (heterosexual vaginal intercourse at least once per month and not sterilized) and seeking contraception
4. Be willing to use either ENG-E2 contraceptive vaginal ring or LNG-EE COC for up to 13 treatment cycles and not intending to use any other forms of contraception (e.g. condoms, except when specified per protocol)

5. Have body mass index of >18 and <38 Kg/m2. Trial sites may exclude subjects with maximum BMI less than 38 kg/m2 based on local standard of care guidelines for the use of combined hormonal contraceptives.
6. Be in good physical and mental health, based upon the medical judgment of the investigator.
7. Be able and will to adhere to use of the ENG-E2 vaginal ring or the LNG-EE COC and to all the required trial procedures, including trial visits and use of the daily diaries and does not plan to relocate during the trial (such that the subject would not be able to continue participation at the trial site).

Exclusion criteria

Cardiovascular risks and disorders:
1. Has a history of venous thromboembolic events (deep vein thrombosis, pulmonary embolism) or history of arterial thrombotic or thromboembolic events or a history of arterial thrombolic events (myocardial infarction, stroke, or peripheral arterial events), or a history or transient ischemia attack or angina pectoris or claudication
2. Is at a higher risk of VTE event due to recent prolonged immobilization (within 2 weeks of screening due to trauma r other illness markedly limiting mobility), plans for surgery requiring prolonged immobilization or has a hereditary or acquired predisposition or elevated risk for venous or arterial thrombosis. Refer to protocol for complete list
3. Is currently smoking or uses tobacco products and is >35 years of age
4. Has uncontrolled or severe hypertension
5. Has a history of severe dyslipoproteinemia
6. 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)
7. Has diabetes mellitus with end organ involvement (nephropathy, retinopathy, neuropathy or vascular involvement) or has had diabetes for > 20 years
8. Has multiple cardiovascular risk factors such as older age (>35 years), obesity, BMI >30 Kg/m2), inadequately controlled hypertension, use of tobacco/nicotine, or inadequately controlled diabetes which in the opinion of the nvestigator in the composite pose an unacceptable risk of participation;Gastrointestinal Disorders:
9. Has a history of pancreatitis associated with severe hyper triglyceridemia
10. Has clinically significant liver disease which is now inactive of successfully treated may be enrolled if liver function values (AST, ALT, total bilirubin) have been normal for the past year and are within the normal range (per central lab) at V1
11. History of malabsorptive bariatric surgery (i.e., bileopancreatic diversion or Roux-en-Y bypass). Non-malabsorptive restrictive surgery is acceptable for inclusion (i.e., Gastric banding, partial gastrectomy);Other Medical Disorders:
12. Has history of malignancy <5years prior to signing informed consent except for treated basal or squamous cell skin cancer or in situ cervical cancer. Subjects with a history or presence of liver tumors (benign or malignant) or sex steroid-influenced malignancies (e.g., of the genital organs or the breasts) are excluded regardless of the timing.
13. Has any disease that may worsen under hormonal treatment, such as disturbances in the bile flow (presence or history of cholestasis, presence of gall stones), systemic lupus

erythematosus, pemphigoid gestationis or idiopathic icterus during a previous pregnancy, middle ear deafness, Sydenham chorea, or porphyria.
14. Has a known allergy/sensitivity or contraindication to the investigational products (ENG-E2 vaginal ring or LNG-EE COC) or their excipients).
15. Has a history (current or within the past two years) of drug or alcohol abuse or dependence.
16. Has any clinically relevant abnormal laboratory result at screening as judged by the investigator.
17. Has a history or current evidence of any condition therapy or other circumstance that in the opinion of the investigator might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject*s participation for the full duration of the trial.;Recent or Current pregnancy:
18. Has a known or suspected pregnancy
19. Has not had at least 2 menstrual cycles following a recent pregnancy
20. Is breast feeding
If recently stopped breast feeding must have resumed normal menstrual cycles.;Gynecologic conditions:
21. Has gonorrhea, chlamydia, or trichomonas, symptomatic vaginitis/cervicitis. Subjects may be screened 3 weeks after completing treatment for these conditions.
22. Has an abnormal cervical smear or positive high risk HPV test at screening or documented within 3 years of screening (i.e. ASCUS-high *risk HPV positive ASC-H, L(G)SIL, H(G)SIL), squamous cell carcinoma, AGUS, AGUS, AGC-neoplastic or AIS)
NOTE: A normal cervical smear within 18 month of trial entry is required in subject 21 years of age and older (or who will become 21 years on the study) or age as recommended by local guidelines for initiation of screening.
23. Is currently using an intra-uterine device or contraceptive implant.
24. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (e.g. bleeding from a cervical polyp, recurrent bleeding after sex).
25. Has stage 4 pelvic organ prolapse (1 cm. beyond intoritus) or lesser degrees of prolapse with a history of difficulty retaining tampons, vaginal rings, or other products in the vagina.;Miscellaneous:
26. Is or has an immediate family member who is part of the investigational site of sponsor staff directly involved with this trial.

Study design

Design

Study phase:	3
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):	01-12-2015
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Microgynon 21
Generic name:	levonorgestrel (LNG)/ethinyl estradiol (EE)
Product type:	Medicine
Brand name:	NA
Generic name:	Etonogestrel/Estradiol (ENG-E2)

Ethics review

Approved WMO Date:	20-10-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2016
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2016
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	EUCTR2014-002208-26-NL
CCMO	NL54724.056.15