A multicenter, randomized, partially blinded, placebo-controlled clinical trial to evaluate the effect on primary dysmenorrheal of vaginal rings with an average daily release of 700 µg nomegestrol acetate (NOMAC) and 300 µg estradiol (E2), or 900 µg nomegestrol acetate (NOMAC) and 300 µg estradiol (E2), or 100 µg etonogestrel (ENG) and 300 µg E2, or 125 µg etonogestrel (ENG) and 300 µg E2

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To identify at least one New Generation Ring that shows clinically relevant treatment efficacy:• in relief of primary dysmenorrhea, as demonstrated by a statistically significantly larger reduction (as compared to baseline) in the mean menstrual...

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

Summary

ID

NL-OMON36928

Source
ToetsingOnline

Brief title
MK8342B-057

Condition

- Other condition

Synonym
pain and/or cramps during menstruation

Health condition

primaire dysmenorroe + reproductive system and breast disorders (menstrual cycle and uterine bleeding disorders)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: MK8342B, Primary dysmenorrhea, Vaginal ring

Outcome measures

Primary outcome

The Primary Efficacy Endpoint is the change in menstrual cramping score based

on item #10 of the MDQ from baseline to the second in-treatment intended

bleeding episode.

The Primary Efficacy Endpoint is related to the Primary Trial Objective.

Secondary outcome

The secondary efficacy endpoints are calculated from baseline through the

second in-treatment intended bleeding episode and concern:

• total mean impact score from baseline through the second in-treatment

intended bleeding episode (total mean impact score is defined as the mean of

the sum of daily responses to questions 5, 7, 8, and 9 in the DysDD)

• total number of tablets of ibuprofen taken

• number of days of intake of ibuprofen

Secondary efficacy endpoints will be analyzed in the same manner as the primary

variable.

Study description

Background summary

NOMAC-E2
The NOMAC-E2 vaginal ring is being studied by Merck to evaluate its efficacy as a contraception method. The vaginal ring is a combined contraceptive vaginal ring that contains the progestogen nomegestrol acetate (NOMAC) and 17-beta estradiol (E2). NOMAC alone (as Lutenyl® 5 mg, and Lutenyl® 3.75 mg) and NOMAC in combination with E2 (as Naemis® 3.75 mg + 1.5 mg) have been approved in the field of hormonal replacement therapy (HRT) for pre- and post-menopausal women. Estradiol is a sex hormone, which is the same as the naturally produced estrogen in females. Estradiol is an approved drug for the treatment of hot flashes and other symptoms of menopause. In addition, both NOMAC and estradiol are components of an approved oral contraceptive (Zoely® / IOA®).

As of May 2012, NOMAC-E2 in the form of a vaginal ring has been used by 71 female subjects between the ages of 18-45 in clinical trials. Multiple doses of NOMAC ranging from 900 micrograms (µg) to 2000 µg per day, and E2 ranging from 50 µg to 300 µg per day, have been administered in these studies to healthy female subjects without safety concern.

ENG-E2
The ENG-E2 vaginal ring is being studied by Merck to evaluate its efficacy as a contraception method. The vaginal ring contains etonogestrel (ENG) and 17-beta estradiol (E2). ENG is a synthetic sex hormone which is a component of several approved drugs for contraception. E2 is a sex hormone, which is the same as the naturally produced estrogen in females. E2 is an approved drug for the treatment of hot flashes and other symptoms of menopause. In addition, E2 is a component of an approved oral contraceptive.

As of April 2012, ENG-E2 in the form of a vaginal ring has been used by 15 female subjects between the ages of 18-45 in a clinical trial. Subjects were administered ENG 120 micrograms (µg) per day with E2 200 µg per day without

safety concern.

Study objective

To identify at least one New Generation Ring that shows clinically relevant treatment efficacy:
• in relief of primary dysmenorrhea, as demonstrated by a statistically significantly larger reduction (as compared to baseline) in the mean menstrual cramping pain score compared to placebo.
The trial will be considered a success if at least one treatment meets the primary objective.

Study design

This is a randomized, placebo-controlled, multicenter, partially-blinded trial of vaginal rings with an average daily release of 700 µg nomegestrol acetate (NOMAC) and 300 µg estradiol (E2), or 900 µg nomegestrol acetate (NOMAC) and 300 µg estradiol (E2), or 100 µg etonogestrel (ENG) and 300 µg E2, or 125 µg etonogestrel (ENG) and 300 µg E2 in female subjects with primary dysmenorrhea.

The trial design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used for the trial.

Each subject will participate in the trial for approximately 5 months from the time the subject signs the Informed Consent Form (ICF) at the beginning of the screening visit through the final study visit. After completion of a baseline, spontaneous, untreated, menstrual cycle, bounded on each end of the cycle by a spontaneous menstruation, during the screening period, each subject will receive assigned treatment for approximately 56 days (two 28-day treatment cycles). After the end of treatment, each subject will be followed for safety monitoring for at least 14 days at which time a final study visit (Visit 5) will be conducted.

Intervention

The nomegestrol acetate (NOMAC) contraceptive vaginal ring (NOMAC-E2-CVR) is an all-EVA (ethylene vinyl acetate) vaginal ring containing estradiol (E2) with an average daily release of 700 µg NOMAC and 300 µg E2, or 900 µg NOMAC and 300 µg E2.

The etonogestrel (ENG) containing contraceptive vaginal ring (ENG-E2-CVR) is also an all-EVA vaginal ring containing E2 with an average daily release of 100 µg ENG and 300 µg E2, or 125 µg ENG and 300 µg E2.

The placebo vaginal ring (PBO-CVR) is an all-EVA vaginal ring with no active ingredients.

Each Investigational Medicinal Product (IMP) (NOMAC-E2, ENG-E2, or Placebo) will be administered for two 28-day periods, each period (treatment cycle) consisting of 21 days of vaginal ring use followed by 7 day vaginal ring-free days.

Study burden and risks

ENG-E2
The overall benefits and risks of combined hormonal contraceptives, including NuvaRing® and Zoely®, also apply to the ENG-E2 vaginal ring. Thus, the general COC contraindications as well as the warnings and precautions in the Summary of Product Characteristics are applicable. These warnings concern amongst others the risk of circulatory disorders (VTE), and breast, cervical, and liver tumors. If a woman has any of the following conditions, she may not be able to place the ENG-E2 vaginal ring correctly or may lose the ring: prolapse of the uterine cervix, cystocele and/or rectocele, or severe or chronic constipation. ENG is the component primarily responsible for ovulation inhibition. The simultaneous administration of EE with ENG in NuvaRing® induces increased SHBG concentrations, which in turn decrease the serum levels of unbound (bioavailable) ENG. Sex Hormone Binding Globulin-induction by E2 is much less and therefore bioavailable ENG serum levels are expected to be higher when using the ENG-E2 vaginal ring. Consequently, the contraceptive action of the ENG-E2 vaginal ring is considered adequate.

NOMAC-E2
The overall benefits and risks of combined hormonal contraceptives, including the NOMAC-E2 oral contraceptive and NuvaRing®, apply to the NOMAC-E2 vaginal ring. Thus, the general COC contraindications as well as the warnings and precautions in the Summary of Product Characteristics are applicable. These warnings concern amongst others the risk of circulatory disorders (VTE), and breast, cervical, and liver tumors. If a woman has any of the following conditions, she may not be able to place the NOMAC-E2 vaginal ring correctly or may lose the ring: prolapse of the uterine cervix, cystocele and/or rectocele, or severe or chronic constipation.

NOMAC is the component primarily responsible for ovulation inhibition. Based on data obtained in the previous NOMAC-E2 vaginal ring study (P307001) the dose of NOMAC (900 µg/day) is considered to be sufficient for ovarian suppression. Additional studies are planned to evaluate contraceptive efficacy. To date, no efficacy studies have been performed with the NOMAC-E2 vaginal ring formulations, therefore contraceptive efficacy can not yet be claimed and subjects should use adequate barrier contraception, such as condoms during the study.

General
NuvaRing® has no adverse effects on the cervix, vagina, and the endometrium, nor did NuvaRing® adversely affect bone mass.

Restoration of fertility is expected to occur rapidly after discontinuation of the NOMAC-E2 vaginal ring, based on the experience with NuvaRing® and NOMAC-E2 containing contraceptives.

Interaction studies with NuvaRing® showed that vaginally administered antimycotics, spermicides, and broad-spectrum antibiotics do not jeopardize the contraceptive efficacy and safety of NuvaRing® and the use of tampons does not affect the concentration of hormones released by NuvaRing®. It is expected that this will also be applicable to the ENG-E2 and NOMAC-E2 vaginal ring. In order to rule out any possible interaction, no concomitant use of these medications was/is allowed for the completed Study 07931 or for the planned studies.

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. Subject must be willing and able to provide written informed consent for the trial.
2. Subject must be female.
3. Subject must be >=18 to <= 50 years of age.
4. Subject must have a body mass index (BMI) >=18 and <=35.
5. Subject must have an established diagnosis of primary dysmenorrhea, characterized by menstrual pain in the absence of detectable pelvic pathology (eg, endometriosis, fibroids, pelvic inflammatory disease).
6. Each non-sterilized sexually active subject of child-bearing potential must agree to use condoms for contraception during the entire screening period, treatment period, and post-treatment period until the final study visit.
7. Subject using a hormonal contraceptive (combined or progestin-only), or a non-hormonal IUD, at the screening visit must agree to stop using that method.
8. Subject has regular menstrual cycles ranging from 24 to 32 days in length (to be confirmed at the randomization visit following completion of a baseline menstrual cycle).

Exclusion criteria

1. Subject has any contraindication to the use of contraceptive steroids.
2. Subject has secondary dysmenorrhea - ie, menstrual pain in the presence of detectable pelvic pathology (eg, endometriosis, fibroids, pelvic inflammatory disease).
3. Subject has not had spontaneous menstruation following a delivery or abortion at the screening visit.
4. The subject is breastfeeding or has not had spontaneous menstruation following completion of breastfeeding at the screening visit.
5. Subject has a history of malignancy <=5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.
6. Subject had a documented abnormal cervical smear result within 6 months prior to the screening visit.
7. Subject routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week, or engages in binge drinking.

Study design

Design

Study phase:	2
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):	01-02-2013
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	etonogestrel - 17β-estradiol contraceptive vaginal ring
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	nomegestrol acetate - 17β-estradiol contraceptive vaginal ring
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	Placebo acetate vaginal ring

Ethics review

Approved WMO Date:	05-09-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-10-2012
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-02-2013
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	EUCTR2012-002449-40-NL
CCMO	NL41841.056.12
Other	Nog niet bekend