A randomized, double-blind, double-dummy, parallel- group, multi-center phase IIb study to assess the efficacy and safety of different dose combinations of an aromatase inhibitor and a progestin in an intravaginal ring versus placebo and leuprorelin / leuprolide acetate in women with symptomatic endometriosis over a 12-week treatment period

Published: 08-09-2014
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- The studymedication in this clinical study was developed for long-term use in patients with endometriosis associated pelvic pain to release the pain and to avoid to otherwise necessary operation.Primary objective-To assess the dose-response...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive tract disorders NEC
Study type	Interventional

Summary

ID

NL-OMON42171

Source
ToetsingOnline

Brief title
ESPARIOS 1

Condition

- Reproductive tract disorders NEC

Synonym
endometriosis, gynecological disorder in the reproductive female system

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer Healthcare AG

Intervention

Keyword: Absolute pain change, dysmenorrhea, Intra-vaginal ring, Symptomatic endometriosis

Outcome measures

Primary outcome

To assess the dose-response relationship and demonstrate efficacy of BAY

98-7196 vs. placebo in women with symptomatic endometriosis

Secondary outcome

- To identify at least 1 superior effective dose of BAY 98-7196 compared to

placebo

- To compare the efficacy of BAY 98-7196 versus leuprorelin / leuprolide

acetate descriptively

- To assess sustainability of treatment effect and recurrence of symptoms

- To evaluate the safety and tolerability of BAY 98-7196 in women with

symptomatic endometriosis

- To explore sub-populations (e.g. subjects with indication for treatment with

a gonadotropin-releasing hormone agonist or surgery as judged by the

investigator or by endometriosis history and symptom severity)

Study description

Background summary

Endometriosis is a benign, estrogen-dependent gynecological disorder affecting 6-10% of reproductive age women. The disease is characterized by the presence of endometrium-like tissue outside the uterine cavity (e.g. the ovaries, peritoneum, rectovaginal space and other pelvic structures).
Dysmenorrhea, chronic pelvic pain, painful intercourse and infertility are the most common symptoms of endometriosis which can have a significant impact on subjects* lives as e.g. substantial morbidity, multiple operations and decreased quality of life. In addition, the economic burden associated with endometriosis treated in referral centers was found to be as high as other chronic diseases like diabetes, Crohn*s disease or rheumatoid arthritis in 10 European countries (2). The high economic burden for the healthcare system was similarly found for the United States (US) (3).
According to guidelines from the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Endocrinology (ESHRE), endometriosis-associated pain is medically treated by agents which are supposed to induce atrophy of endometriotic lesions such as combined oral contraceptives (COCs), progestins, danazol, and gonadotropin-releasing hormone (GnRH) analogues (4,5). These treatment options are not considered significantly different in terms of efficacy (1). Side effect profiles and costs, however, differ considerably. Thus, COCs, although not approved for the indication, are commonly used *off label* for the treatment of endometriosis.
In contrast, different progestins are approved in different countries for the treatment of endometriosis, but are used to a much lower extent compared to COCs.
Due to the lack of other effective medical treatments, after failure of COC or progestin treatment there are currently no alternatives available for subjects with endometriosis-associated pain which could be used long-term. GnRH analogues have an unfavorable side-effect profile (e.g. hot flushes, bone loss) and can only be used short term. Danazol is rarely used in clinical practice, due to its side effect profile (e.g. acne, weight gain, hirsutism, voice changes). Surgery, as the last option is associated with the inherent risk of complications and a substantial relapse rate over time which is reported to range from up to 50% - 75% after 2-5 years (6,1). Thus, there is a high medical need for an efficacious, safe and tolerable treatment which could be used long-term for women with symptomatic endometriosis, and especially for those not sufficiently responding to COCs or progestins. To fill the gap of available treatment options, Bayer seeks to develop anastrozole (ATZ) combined with levonorgestrel (LNG) in an intravaginal ring (IVR; BAY 98-7196) for subjects

with endometriosis-associated pain which could be used for long-term treatment and potentially avoid otherwise necessary surgeries.

Study objective

- The studymedication in this clinical study was developed for long-term use in patients with endometriosis associated pelvic pain to release the pain and to avoid to otherwise necessary operation.

Primary objective
-To assess the dose-response relationship and demonstrate efficacy of BAY 98-7196 vs. placebo in women with symptomatic endometriosis

Secundairy objectives
- To identify at least 1 superior effective dose of BAY 98-7196 compared to placebo
- To compare the efficacy of BAY 98-7196 versus leuprorelin / leuprolide acetate descriptively
- To assess sustainability of treatment effect and recurrence of symptoms
- To evaluate the safety and tolerability of BAY 98-7196 in women with symptomatic endometriosis
- To explore sub-populations (e.g. subjects with indication for treatment with a gonadotropin-releasing hormone agonist or surgery as judged by the investigator or by endometriosis history and symptom severity)
- collecting data on the effect of the intra-vaginal ring on the condoms and condoms use.

Study design

it concerns a randomized, double-blind, double-dummy, parallel-group, multi-center phase IIb study to assess the efficacy and safety of different dose combinations of an aromatase inhibitor and a progestin in an intravaginal ring versus placebo and leuprorelin / leuprolide acetate in women with symptomatic endometriosis over a 12-week treatment period
All patients will be randomized in 6 different treatment arms in the ratio of 1:1:1:1:1:1 and all patients will receive an intra-vaginal ring and the intramuscular injection.
The following arms were created:
1. Placebo A IVR + placebo intramuscular (i.m.) injection
2. LNG 170 mg IVR + placebo i.m.
injection; --> dose per day:
LNG (40µg)
3. ATZ 50 mg+ LNG 170 mg IVR + placebo i.m. injection;
--> dose per day: ATZ (300 µg) + LNG (40 µg)
4. ATZ 120 mg+ LNG 170 mg IVR + placebo i.m. injection:
--> dose per day: ATZ (600 µg) + LNG (40 µg)

5. ATZ 200 mg+ LNG 170 mg IVR + placebo i.m. injection:
--> dose per day: ATZ (1050 µg) + LNG (40 µg)
6. Placebo B IVR + leuprorelin / leuprolide acetate (11.25 mg - 3-month depot) i.m. injection

Intervention

The following arms were created:
1. Placebo A IVR + placebo intramuscular (i.m.) injection
2. LNG 170 mg IVR + placebo i.m.
injection; --> dose per day:
LNG (40µg)
3. ATZ 50 mg+ LNG 170 mg IVR + placebo i.m. injection;
--> dose per day: ATZ (300 µg) + LNG (40 µg)
4. ATZ 120 mg+ LNG 170 mg IVR + placebo i.m. injection:
--> dose per day: ATZ (600 µg) + LNG (40 µg)
5. ATZ 200 mg+ LNG 170 mg IVR + placebo i.m. injection:
--> dose per day: ATZ (1050 µg) + LNG (40 µg)
6. Placebo B IVR + leuprorelin / leuprolide acetate (11.25 mg - 3-month depot) i.m. injection

Study burden and risks

There are at maximum 7 visits
The patient is asked to complete 2 questionnaires to score the pain the patient is experiencing (NRS and VAS). Next to these painscore-questionnaires, the patient is asked complete 5 times 2 questionnaires and 4 times 3 questionnaires. All questionnaires evaluate the current health-status and the pain of the patient. All questionnaires will be completed electronically.
The evaluate the every day status, the patient is asked to keep an electronic diary.
The patient will receive a full physical examination (length, bloodpressure, heartrate and temperature, etc) and gynecological examination.
The research personnel will contact the patient on a weekly basis form visit 3 until the end of the study to ask about the condoms and the condom-usage. The patient will be asked whether there were any issue as slippages, breakages, leakages or any other problems.

Contacts

Public
Bayer

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NL
Scientific
Bayer

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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. Signed and dated informed consent.
2. Premenopausal women18 years and above at the time of screening.
3. Women with endometriosis confirmed by laparoscopy or laparotomy within the last ten years but not less than 8 weeks before the screening visit
In Japan, diagnosis based on imaging (transvaginal ultrasound or MRI) also qualifies for inclusion.
4. Moderate to severe endometriosis-associated pelvic pain (EAPP) of >=5 in the last 28 days before screening visit 1 measured on the numeric rating scale (NRS; i.e. 4-week recall period).
5. At randomization: Adherence to the study procedures during the screening period, at least 24 diary entries of ESD item 1 during the last 28 consecutive days before the randomization visit, and a sum of the available ESD item 1 (*worst pain* on the daily NRS) entries during this period of at least 98 (corresponding to an average score of >= 3.5).
6. Willingness to use only ibuprofen as rescue pain medication for EAPP, if needed according to investigator*s instruction.
7. Use of a non-hormonal barrier method (i.e. spermicide-coated condoms) for contraception from screening visit until the end of the study. This is not required if adequate contraception is achieved by vasectomy of the partner.

Exclusion criteria

1. Pregnancy or lactation (less than three months since delivery, abortion, or lactation before start of treatment)
2. Any diseases or conditions that can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study drug
3. Any diseases or conditions that might interfere with the conduct of the study or the interpretation of the results.
4. Any disease or condition that may worsen under hormonal treatment according to the assessment and opinion of the investigator.
5. Undiagnosed abnormal genital bleeding
6. Wish for pregnancy during the study
7. Regular use of pain medication due to other underlying diseases
8. Non-responsiveness of endometriosis associated pelvic pain (EAPP) to GnRH-a or surgery (partial response is not exclusionary).

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):	21-01-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BAY98-7196
Generic name:	BAY98-7196

Ethics review

Approved WMO Date:	08-09-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-11-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-005090-53-NL
CCMO	NL50222.100.14