Multi-center, randomized, comparator-controlled, single-blind, parallel-group study to investigate the pharmacodynamics, pharmacokinetics and safety of an intrauterine system releasing BAY 1007626, as compared with Mirena and Jaydess, in a combined proof-of-concept and dose-finding study in healthy pre-menopausal women treated for 90 days

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The primary objective of this study is to investigate local and systemic effects of BAY 1007626 on:- Number of bleeding and spotting days,- Endometrial histology,- Ovulation (as surrogate for systemic effects).The secondary objective of this study…

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

Summary

ID

NL-OMON42633

Source
ToetsingOnline

Brief title
BAY 1007626 / 15731

Condition

- Other condition

Synonym
contraception, fertility control

Health condition

contraception

Research involving
Human

Sponsors and support

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

Intervention

Keyword: contraception, dose finding, intrauterine system, pharmacodynamics

Outcome measures

Primary outcome

The primary objective of this study is to investigate local and systemic

effects of BAY 1007626 on:

- Number of bleeding and spotting days,

- Endometrial histology,

- Ovulation (as surrogate for systemic effects).

Secondary outcome

The secondary objective of this study is to assess the effects of BAY 1007626

on:

- Endometrial thickness,

- Bleeding characterization (intensity and pattern),

- Serum levels of hormones (estradiol, progesterone,luteinizing hormone,

follicle-stimulating hormone),

- Cervix function (Insler score),

- Safety and tolerability (treatment emergent adverse events and SAE),

- Pharmacokinetics (PK) following intrauterine application of BAY 1007626.

Study description

Background summary

There is a continuing need for innovation in the field of safe and reliable contraception. At present, there is a trend towards more widespread use of long-acting reversible contraceptive (LARC) methods. Levonorgestrel-releasing intrauterine systems (IUSs) are in wide use because of their high efficacy, cost effectiveness and convenience compared with short-acting methods. However, such systems are frequently associated with an increased incidence of bleeding and spotting during the first few months of treatment, and long-term use can lead to amenorrhea (although many women regard this as a positive effect) and to systemic effects such as inhibition of ovulation, occasional development of ovarian cysts and also partial androgenic activity.

BAY 1007626 is a synthetic hormone with progesterone-like effects, a so-called progestin. It is being developed for use in a new intrauterine delivery system for reversible, long-acting contraception. This new LARC is intended to show equal contraceptive efficacy (based on surrogate marker endometrial histology), reduce the initial bleeding and spotting, and result in a lower incidence / frequency of systemic effects on ovarian activity (ovulation inhibition) compared with Levonorgestrel-releasing intrauterine systems (LNG-IUSs, such as Mirena).

In animal studies, BAY 1007626 showed a high plasma clearance and therefore low systemic exposure. The phase I study 15728 confirmed that BAY 1007626 has a higher plasma clearance and lower systemic exposure compared to Mirena. The hypothesis is that low systemic exposure should result in fewer systemic

adverse events in humans (e.g., ovulation inhibition, ovarian cysts), even at relatively high release rates, and would thus make possible a high local (uterine) progestin exposure resulting in an improved bleeding profile compared with that of Levonorgestrel-releasing IUSs.

Study objective

The primary objective of this study is to investigate local and systemic effects of BAY 1007626 on:
- Number of bleeding and spotting days,
- Endometrial histology,
- Ovulation (as surrogate for systemic effects).

The secondary objective of this study is to assess the effects of BAY 1007626 on:
- Endometrial thickness,
- Serum levels of hormones: estradiol (E2), progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH),
- Cervix function (Insler score),
- Bleeding pattern characterization,
- Safety and tolerability of BAY 1007626,
- PK of BAY 1007626 following intrauterine application, in comparison with Jaydess and Mirena.

Study design

The study will be conducted in a multi-center, randomized, comparator-controlled, parallelgroup, single-blind design in healthy women aged 18-40 years. Six different types of IUS will be used: four with different release rates of BAY 1007626 and two comparators (Jaydess and Mirena). Each of these will be applied for 90 days. The subjects will additionally be required to use non-hormonal contraception, as this is the first study for investigation of contraceptive effects as measured by local endometrial effects. It is planned that a total of 176 subjects will take part in the study: 33 in each of the BAY 1007626 and the Mirena treatment arms, and 11 in the Jaydess treatment arm.

The frequency and pattern of bleedings as well as endometrial histology will be assessed for all women:

- The number of bleeding and spotting days will be evaluated using an electronic diary.
- Endometrial histology will be evaluated in endometrial biopsy specimen to be taken in the pre-treatment cycle and around the end of treatment phase as well as during follow-up. The histology of the specimen will be evaluated by blinded reading involving three pathologists.

The evaluation of ovarian activity under treatment will be assessed in all women as follows:

- In the dense visit subgroup a thorough analysis, requiring a high frequency of study visits, will be done. Here ovarian activity will be assessed based on twice weekly measurement of size of follicle-like structures (FLS) by TVUS and serum progesterone and estradiol concentrations using the 6-step grading of ovarian activity according to Hoogland. The dense visit subgroup will consist of 12-18 subjects per treatment arm for BAY 1007626 and Mirena and of all 11 subjects receiving Jaydess. As these investigations will require a twice weekly visit schedule they will be limited to a small number of preselected study sites.

- In the weekly visit subgroup (N = 15-21 subjects per treatment arm, except for the Jaydess arm) ovulation will be assessed by analysis of progesterone serum concentrations. A progesterone serum concentration above 5 nmol/L has been defined as indicating ovulation.

The effects on cervical mucus (Insler score) will be evaluated only in the dense visit group population. The aim is to have in this subgroup, at the end of the study, at least 10 evaluable women from each of the treatment arms receiving the various dose levels of BAY 1007626 or Mirena and 8 of those receiving Jaydess.

Pharmacokinetics (PK) of BAY 1007626 will be evaluated using sparse sampling and a population PK approach in the women with weekly visit schedule. A more detailed PK profile will be obtained in the women of the dense visit subgroup.

Further safety data i.e. a panel of safety laboratory parameters, vital signs (blood pressure, heart rate and body weight) as well as 12 lead ECG will be collected in all women.

Intervention

The new product to be tested is a *New Progestin Intrauterine System* (NP IUS). The active drug substance is BAY 1007626. The two comparators are standard, commercially available products ((Jaydess / Mirena).

Study burden and risks

BAY 1007626 has not been administered to women released from an IUS, yet. However, 50 women beyond child bearing age received BAY 1007626 administered either subcutaneously or intravenously. The following temporary side effects with BAY 1002076 were observed in this first human study:

• Headache

• Changes in laboratory values which did not give rise to any concern about the safety (e.g. kidney function test, lipid metabolism)
• Exhaustion
• Hot flushes
• Blood in the urine
• Injection site reaction

Some other side effects such as diarrhoea, vomiting and breast discomfort only occured in single volunteers.

Based on the aforementioned clinical study and several studies in e.g. animals, BAY1007626 is assessed as sufficiently well characterized and as safe for a first clinical study in women of child-bearing potential with a treatment period of 90 days.

There is no human experience so far from BAY 1007626 IUS users. As reported for intrauterine contraceptives (Mirena® and Jaydess®) comparable side effects can be expected such as
infrequent bleeding, pelvic inflammation, expulsion of the IUS, perforation of the womb and ovarian cysts.

Both Mirena® and Jaydess® are levonorgestrel releasing intrauterine systems for contraception available on the market. The following side effects have been reported with Mirena® and Jaydess® respectively.

Very common side effects (>=1/10 study subjects have experienced these side effects):

- Mirena®: headache, abdominal / pelvic pain, bleeding changes including increased and decreased menstrual bleeding, spotting, infrequent or very light bleeding or absent of menstrual bleeding, inflammation of the vulva and vagina (vulvovaginitis), genital discharge.
- Jaydess®: headache, abdominal/pelvic pain, acne/greasy skin, bleeding changes including increased and decreased menstrual bleeding, spotting, infrequent or very light bleeding or absent of menstrual bleeding, ovarian cyst, inflammation of the vulva and vagina (vulvovaginitis)

Common side effects (>=1/100 to < 1/10 study subjects have experienced these side effects):
- Mirena®: ovarian cyst, painful periods, depression/ depressed mood, migraine, back pain, nausea, acne, increased growth of hair on the face and body, painful breasts, intra-uterine contraceptive device expelled, upper genital tract infection.
- Jaydess®: depressed mood/depression, migraine, nausea, hair loss, upper genital tract infection, painful menstruation, breast pain/discomfort, device expulsion, genital discharge.

Uncommon side effects (>=1/1,000 to < 1/100 study subjects have experienced these side effects):
- Mirena: hair loss
- Jaydess®: excessive body hair.

Rare side effects (>=1/10,000 to < 1/1,000 study subjects have experienced these side effects):
- Mirena®: perforation of the womb
- Jaydess®: perforation of the womb.

Side effects of unknow frequency:
- Mirena®: allergic reaction (symptoms may include rash, hives (urticaria) and angioedema (characterised by sudden swelling of e.g. the eyes, mouth, throat), increased blood pressure.

Contacts

Public
Bayer

Sellerstr. 31
Berlin 13353
DE
Scientific
Bayer

Sellerstr. 31
Berlin 13353
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Healthy female subjects

Exclusion criteria

Criteria which in the opinion of the investigator preclude participation for scientific reasons or because of the subject*s safety.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-07-2015
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	BAY 1007626
Product type:	Medicine

Brand name:	LEVONORGESTREL
Generic name:	Jaydess
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	LEVONORGESTREL
Generic name:	Mirena
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-05-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-05-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2015
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	EUCTR2013-003980-74-NL
CCMO	NL52946.056.15