Multicentre, Open-Label Trial to Assess the Safety and Tolerability of LF111 (Drospirenone 4.0 mg) Over 6 Cycles in Female Adolescents, With a 7-Cycle Extension Phase

Published: 07-02-2014
Last updated: 20-04-2024

It is expected that LF111 will offer benefits to adults in the form of efficacy similar to COCPs, absence of estrogen-related risks, reduced tendency to weight gain and extended dosing window. It is likely that adolescents will share these benefits...

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON40539

Source
ToetsingOnline

Brief title
CF111/304

Condition

- Other condition

Synonym
contraception, fertility control

Health condition

contraception

Research involving
Human

Sponsors and support

Primary sponsor: Laboratorios León Farma S.A
Source(s) of monetary or material Support: León Farma S.A.

Intervention

Keyword: bleeding pattern, oral contraception, progestogen only pill, safety and tolerability

Outcome measures

Primary outcome

The objective of this trial is to evaluate safety and tolerability, including

bleeding pattern

Safety endpoints: Treatment-emergent adverse events, Vital signs and Clinical

laboratory parameters

Tolerability endpoint: Vaginal bleeding pattern during treatment cycles 1-6

(subject diaries)

Other endpoint: IMP acceptability

Secondary outcome

n.a.

Study description

Background summary

Drospirenone (DRSP) is a fourth generation progestogen, which is derived from spironolactone. DRSP has a pharmacological profile similar to natural progesterone and possesses anti-mineralocorticoid and anti-androgenic activity.

In combination with ethinyl estradiol (EE) and 17B-estradiol (E2), DRSP has been extensively studied in the preclinical and clinical setting. DRSP 3 mg in combination with EE 30 microgram or 20 microgram, from 21 days to 24 days, is registered for use in the prevention of pregnancy as an oral contraceptive, (e.g. Yasmin®, Yasminelle®, YAZ®). In addition, DRSP is registered for use in combination with E2 1 mg as Angeliq®[3] (in Europe at 2 mg and in the USA at 0.5 mg) as hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women and the prevention of postmenopausal osteoporosis in women who are intolerant to or contraindicated for other medicinal products approved for the prevention of osteoporosis.

Leon Farma has developed a new formulation with 4.0 mg of DRSP (LF111). This formulation has been tested in a pharmacokinetic (PK) study in comparison with a drospirenone-containing COCP on the market. PK study CF111/103A confirmed that absorption after a single dose is higher with the 4.0 mg drospirenone compared to standard products on the market containing 3.0 mg drospirenone (YAZ). However, after multiple-dose administration in study CF111/103A, the relative bioavailability was found to be only 76.51% for LF111 compared to YAZ, indicating that there is an influence of ethinyl estradiol on the PK of drospirenone. Ovulation inhibition with LF111 was confirmed and maintained despite delaying two pills for 24 hours.

The dosing regimen of the POPs currently on the market is to take verum tablets continuously with no placebo tablets or gaps between packs. Unscheduled bleeding is a major reason for discontinuing these POPs. Mechanisms relevant to uterine bleeding are complex and novel strategies to manage these significant problems are needed. LF111 is a new POP formulation with a new regimen of 24 verum tablets followed by 4 placebo tablets, designed to try to reduce unscheduled bleeding.

Overall, 1527 healthy volunteers have been enrolled into the LF111 clinical programme, of which approximately 1332 subjects have received LF111. In total, 116 subjects participated in the phase I programme, 146 subjects were enrolled into the phase II and 1265 subjects have been enrolled into the phase III studies. There is no indication that the safety profile of DRSP would be altered when given alone without EE or E2. In the pivotal trial CF111-301 the contraceptive efficacy of LF111 was demonstrated with an overall Pearl Index [95% CI] of 0.5106 [0.1053; 1.4922]

Study objective

It is expected that LF111 will offer benefits to adults in the form of efficacy similar to COCPs, absence of estrogen-related risks, reduced tendency to weight gain and extended dosing window. It is likely that adolescents will share these benefits. However, LF111 has no particular features that would make it particularly appropriate in this age group, as the risks associated with the estrogen component of COCPs are generally perceived as very low in this age

group and it is these products that are routinely prescribed to teenage girls seeking contraception.

As agreed on with the EMA, the current study intends to evaluate the safety and tolerability, including bleeding pattern, of LF111 (4.0 mg DRSP) in approximately 100 adolescents

Study design

Multicentre, open-label, phase-III safety trial in female adolescents aged 12-17 years. (In some countries the lower age limit may be higher due to national legislation.) After six treatment cycles the subjects may continue with the seven-cycle extension phase.

The trial will consist of a screening visit (V1a), an IMP dispensing visit (V1b), six 28-day treatment cycles with five on-site visits (V2, V3, V4, V5 and V6/EDV) and a follow-up visit V FU, 10-14 days after last IMP intake. For subjects participating in the extension phase and continuing IMP intake during treatment cycles 7-13, two additional visits will be performed before V FU: telephone visit V7 and on-site visit V8/EDV

Intervention

The study will start with a screening visit. During the screening visit standard medical assessments including safety laboratory tests (blood draw, urine collection, pregnancy test), a physical examination, a gynaecological examination (If the hymen is intact, no vaginoscopy and no intravaginal ultrasound will be performed) and a vital signs measurement will be performed.

If the subject is considered eligible, the subject will be enrolled in the study

During study the subjects will visit the unit 6 times (day of treatment allocation,14 days after, start cycle 2, start cycle 3, start cycle 5 and end of cycle 6) . Subjects will also complete a bleeding diary daily. If the subject participates in the extension phase, the subject will have 1 follow-up call start of cycle 10 and 1 visit end of cycle 13.

A final follow-up visit will be performed.

During the visits the subjects will be asked for possible side effects, a pregnancy test will be perfomed and vital signs will be checked, at V6 and V8 (if applicable) blood will be drawn and urine collected for safety, a pregnancy test will be perfomed and a physical and a gynaecological examination will be conducted

Study burden and risks

LF111 is a new contraceptive formulation and there is a certain risk that it might be not as effective as other oral contraceptives that are already on the market. Therefore, there is a risk to get pregnant during the trial. As with any other drugs, this trial medication has the potential to cause side effects. Their influence on the subjects health can vary from symptoms that cause the subject to have mild discomfort to more severe conditions that will require treatment.

The side effect profile of DRSP (LF111) given alone is not fully elucidated. When given in combination with ethinyl estradiol or estradiol the most common events that have been reported in more than 1% of subjects in the pivotal clinical studies include, which may or may not be drug-related: Upper respiratory infection, headache, breast pain, vaginal yeast infection (moniliasis), vaginal discharge (leukorrhea), diarrhea, nausea, vomiting, vaginitis, abdominal pain, flu syndrome, painful menstruation (dysmenorrhea), allergic reaction, urinary tract infection, accidental injury, bladder infection (cystitis), tooth disorder, sore throat (pharyngitis), infection, fever, surgery, sinusitis, back pain, emotional lability, migraine, Pap smear (microscopic examination of cervical cells) suspicious, indigestion (dyspepsia), rhinitis, acne, gastric flu (gastroenteritis), bronchitis, inflammation of the throat (pharyngitis), skin disorder, intermenstrual bleeding, libido decreased, weight gain, pain, depression, cough increased, dizziness, menstrual disorder, pain in extremity, pelvic pain, and weakness (asthenia).

The use of combination oral contraceptives is associated with increased risks of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, stroke), liver tumor, gallbladder disease, and high blood pressure. The risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as high blood pressure, high cholesterol levels, obesity, diabetes and smoking. The risk of venous thromboembolic events with the use of DRSP alone is not yet known.

The subjects will be closely monitored. The subjects will be regularly questioned for any side effects. The subjects will be asked to report, as soon as possible, any changes in physical and/or mental well being

Contacts

Public
Laboratorios León Farma S.A

Polígono Industrial de Navatejera, La Vallina s/n -
Villaquilambre, León 24008
ES
Scientific
Laboratorios León Farma S.A

Polígono Industrial de Navatejera, La Vallina s/n -
Villaquilambre, León 24008
ES

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

Female adolescents aged 12-17 years and postmenarcheal for at least six months

Exclusion criteria

Known contraindication or hypersensitivity to ingredients or excipients of IMP

Study design

Design

Study phase:	3
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	Drospirenone

Ethics review

Approved WMO

Date:	07-02-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	14-03-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2013-005234-37-NL
CCMO	NL47471.000.14