

2. PROTOCOL SYNOPSIS

Name of sponsor/company: Laboratorios León Farma S.A.	
Name of active ingredient: Drospirenone (DRSP)	
Title of trial: A Pivotal, Multicenter, Non-Comparative Trial on the Contraceptive Efficacy, Safety, Tolerability and Pharmacokinetics of LF111 (Drospirenone 4.0 mg) During 13 Cycles	
Trial number: CF111/303	
IND number: 111347	
Coordinating investigator: Prof. David F. Archer, MD	
Trial center(s): Approximately 40 centers located in the United States of America	
Planned duration of the trial: First subject first visit: October 2014 Last subject last visit: July 2017	Phase of development: III
Subject recruitment: 20 months	
Objectives: Primary: To demonstrate the contraceptive efficacy of LF111 Secondary: To demonstrate the safety and tolerability of LF111 and assess the pharmacokinetics of LF111	
Methods / trial design: This trial is a prospective, multicenter, open-label, non-controlled trial in female subjects, age 15 and above who present to the clinic seeking contraception, who are postmenarcheal and premenopausal. Breastfeeding women are allowed to participate in the trial. At V1a (screening), informed consent/assent will be obtained and the screening procedures will be performed. At V1b, after the results of the laboratory tests have confirmed the subject's eligibility, the subject will be provided with the investigational medicinal product (IMP) and an electronic diary and the subject will be instructed in their use. Afterwards, the subjects will attend Visits 2 to 5 at Day 20±2 of the 1 st , 3 rd , 6 th and 9 th cycle and Visit 6 at Day 29+2 of the 13 th cycle. The follow-up (Visit 7) will take place 10-14 days after Visit 6. Once a month, on Day 10 (+ 2 days) of each cycle, the subjects will be contacted by the site staff to collect information on any adverse events which might have occurred. The trial will include women who have never used hormonal contraceptives before consent/assent (naïve users), women who have not used hormonal contraceptives in the past three months before consent/assent or who have used hormonal contraceptives in the past but have a contraceptive-free time of less than three months before consent/assent (previous users) as well as women directly switching from another hormonal method (switchers). Women who have used hormonal contraceptives in the past but have a contraceptive-free time of less than three months before consent/assent are allowed to be included into the trial if they had at least one complete menstrual cycle before enrollment. For naïve users and previous users, the first IMP intake will be on the first day of the next menstrual bleeding after Visit V1b. (If the menstrual bleeding starts in the evening, and the subject prefers to take her pill in the morning, then she may begin the first IMP intake the next day [Day 2 of the menstrual bleeding]). For a switcher, the first IMP intake will be on	

the day following the last active pill of the previous hormonal contraceptive. The subject is free to choose an intake time in the morning or evening that suits her requirements.

Breastfeeding women can start the first IMP any day starting six weeks after delivery.

A population pharmacokinetic (PK) analysis planned in the whole subject population, will obtain sparse blood samples to determine plasma concentrations of LF111 at Visits 2 and 4. In total, four blood samples will be collected: two samples each will be collected during the 1st cycle (Visit 2: Cycle 1, Week 3, Day 20±2) and during the 6th cycle (Visit 4: Cycle 6, Week 3, Day 20±2) of treatment.

Number of subjects (planned):

Screened (enrolled): Approximately 1500. Screening will continue until a sufficient number of subjects have been allocated to treatment.

Allocated to treatment: At least 995 non-breastfeeding subjects, including a minimum of 75 subjects > 35 years.

Note: Breastfeeding women are also allowed to be enrolled in the trial.

Collected medication cycles: At least 5000 evaluable cycles (cycles with intercourse without back-up contraceptive at least once per month based on electronic diary question 'Did you have sexual intercourse since the beginning of the cycle?') for non-breastfeeding subjects aged ≤ 35 years (at the time of trial enrollment).

At least 200 women having completed 13 cycles of treatment will be analyzed for safety.

Diagnosis and main criteria for inclusion:

1. Sexually active, postmenarcheal and premenopausal female subjects at risk of pregnancy including breastfeeding women with no upper age limit.
2. Female subjects at risk of pregnancy, between the ages of 15 and 17 (inclusive) provided that
 - Applicable national, state and local laws allow subjects in this age group to consent/assent to receive contraceptive services, and
 - All applicable laws and regulations regarding the informed consent/assent of the subjects to participate in clinical trials are observed.
3. Regular cycles during the last six months before consent/assent when not using hormonal contraception.
4. At least three complete menstrual cycles after delivery (only applicable for women who were pregnant within the last six months and for non-breastfeeding women).
Breastfeeding women can be included six weeks after delivery irrespective of menstrual cycles post-delivery.
5. At screening, maximum systolic blood pressure (median value of three values) ≤ 159 mm Hg and diastolic blood pressure (median value of three values) ≤ 99 mm Hg.
6. Be able and willing to provide written informed consent or assent if the subject is adolescent, prior to undergoing any trial-related procedure.
7. Willing to use trial contraception for thirteen 28-day cycles.
8. Be willing to have intercourse each cycle of trial without the need to use back-up

contraceptive.

9. Be willing to state that, to her best knowledge, her male sexual partner(s):
 - Has not had a vasectomy or been previously diagnosed as infertile.
 - Has not been previously diagnosed or suspected of human immunodeficiency virus (HIV) unless he has subsequently had a negative HIV test.
 - Has not been known to have engaged in homosexual intercourse in the past five years unless he has had negative HIV test results since then.
 - Has not shared injection drug needles in the past unless he has had a negative HIV test at least six weeks since last use.
10. Agree not to participate in any other clinical trials during the course of this trial.

Exclusion criteria:

1. Pregnant.
2. Subject is known to or suspected of not being able to comply with the trial protocol, the use of the trial medication or the use of the trial diary.
3. History of infertility.
4. Abnormal finding on pelvic, breast or ultrasound examination that in the investigator's opinion contraindicates participation in the trial.
5. Unexplained amenorrhea.
6. Known polycystic ovary syndrome.
7. Women ≥ 21 years of age with a Papanicolaou (pap) smear reading LGSIL or higher at screening (or six months prior to screening date). Human papilloma virus (HPV) testing in subjects with atypical squamous cells of undetermined significance (ASC-US) can be used as an adjunctive test.
 - Subjects with ASC-US can be included if they are negative for high-risk HPV strains.
 - Subjects < 21 years of age do not require a pap smear.
8. Known contraindication or hypersensitivity to ingredients or excipients of the IMP, including:
 - a. Renal insufficiency
 - b. Hepatic dysfunction
 - c. Adrenal insufficiency
 - d. Current or history of venous thrombophlebitis or thromboembolic disorders (venous thrombembolism, which includes deep vein thrombosis and pulmonary embolism)
 - e. Current or history of cerebral-vascular or coronary-artery disease
 - f. Valvular heart disease with thrombogenic complications
 - g. Diabetes with vascular involvement
 - h. Headaches with focal neurological symptoms
 - i. Major surgery with prolonged immobilization

- j. Known or suspected carcinoma of the breast
- k. Known or suspected sex-steroid sensitive malignancies
- l. Undiagnosed abnormal genital bleeding
- m. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- n. Liver tumor (benign or malignant) or active clinically significant liver disease.
- 9. Uncontrolled thyroid disorder (i.e., on stable dose of thyroid replacement for less than two months).
- 10. Uncontrolled concomitant diseases (i.e., not on a stable treatment dose for at least two months).
- 11. Evidence or history of alcohol, medication or drug abuse (within the last 12 months prior to consent/assent).
- 12. Known inherited or acquired predisposition to venous thromboembolism or arterial thromboembolism (e.g., factor V_{Leiden}, Prothrombin mutation, Antiphospholipid-antibodies) or bruising within the last 12 months prior to consent/assent.
- 13. Known or suspected HIV and/or hepatitis infection at screening.
- 14. Received a dose of depot medroxyprogesterone acetate (DMPA or Depo-Provera[®]) during the 10 months prior to consent/assent, or received any combined injectable contraceptive (e.g., Cyclofem[®]) during the six months prior to consent/assent, or no spontaneous menses since last injection.
- 15. Long-term treatment (longer than seven consecutive days within a month prior to V1b) of any medication that might interfere with the efficacy of hormonal contraceptives.
Prohibited medication include:
 - a. Anticonvulsants (e.g. phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, primidone)
 - b. Barbiturates
 - c. Rifampin
 - d. Bosentan
 - e. Griseofulvin
 - f. St. John's wort (*hypericum perforatum*)

16. Administration of human chorionic gonadotropin (hCG) or intake of co-medication containing hCG within a month prior to V1b).
17. Progestin-releasing intra-uterine device (IUD) or contraceptive implant received or in place within the last two months prior to consent/assent.
18. Planned regular concomitant use of barrier contraceptive methods, spermicides, IUDs or other contraceptive measures (excepting occasional use for safety reasons, e.g., to reduce risk of infection).
19. Evidence or history of clinically significant psychiatric illness or suicide risk.
20. Participation in another trial of an investigational drug or device parallel to the current trial or less than 90 days before consent/assent, or previous participation in the current trial and dispensed trial medication.
21. Subject is a member of the investigator's or Sponsor's staff or a relative or family member thereof.
22. Any condition that, in the opinion of the investigator, may jeopardize protocol compliance or the scientific integrity of the trial.

Duration of treatment for the individual subject: 13 sequential cycles of 28 days

Test product, dose and mode of administration:

LF111 coated tablets (4.0 mg drospirenone), oral administration

Reference therapy, dose and mode of administration: Not applicable.

Criteria for evaluation:

Efficacy:

Primary:

- Pearl index (PI) from evaluable cycles in non-breastfeeding women aged ≤ 35 years (at the time of trial enrollment)

Secondary:

- Pearl Index based on overall cycles (overall PI) in women aged ≤ 35 years (at the time of trial enrollment)
- PI for method failures in women aged ≤ 35 years (at the time of trial enrollment)
- Pregnancy ratio in women aged ≤ 35 years (at the time of trial enrollment)
- Overall PI, PI for method failures, PI (using evaluable cycles) and pregnancy ratio (life table analysis) in all women
- Overall PI, PI for method failures, PI (using evaluable cycles) and pregnancy ratio (life table analysis) in women aged > 35 years

Data from breastfeeding women will be excluded from the efficacy analyses but included in the analyses regarding safety and tolerability.

Safety/Tolerability:

- Adverse events (AEs)

- Vital signs
- Clinical laboratory parameters
- Vaginal bleeding pattern
- IMP acceptability

Pharmacokinetics:

- DRSP plasma concentrations
- Area under the curve (AUC)
- Volume of distribution
- Apparent clearance

Statistical methods:**Statistical analysis:**

Analysis of the primary efficacy variable defined as PI based on evaluable cycles in non-breastfeeding women aged ≤ 35 years (at the time of trial enrollment) will be performed for the Full Analysis Set (FAS). Two-sided 95% confidence interval (CI) for the PI will be calculated assuming that events of pregnancy have a Poisson distribution.

Secondary efficacy analysis will be based on the FAS. Two-sided 95% CIs will be calculated for the overall PI and the method failures PI.

Life table analysis: The pregnancy rate at each cycle and the cumulative pregnancy rate will be calculated (95% CI).

Analysis of safety endpoints will be conducted using the Safety Set only.

All adverse events (AEs) and treatment-emergent AEs (TEAEs) will be summarized by calculating the number and percent of subjects with AEs by preferred term and system organ class. Also TEAEs will be summarized by severity and relationship to treatment. Number and percent of TEAEs leading to trial termination will be provided.

Laboratory parameters will be summarized by calculating summary statistics on the absolute values and on the change from V1a to V3, V4, V5 and V6. Shift tables will be provided to illustrate changes with respect to the laboratory normal ranges between V1a and V6 (or EDV). The number and percent of subjects with values outside the limits of clinical significance will be summarized.

Analysis of tolerability will be based on FAS.

Number and percent of subjects with bleeding and spotting, scheduled bleeding, scheduled spotting, unscheduled bleeding and unscheduled spotting will be presented for each cycle. The Clopper-Pearson 95% confidence interval for rate of subjects will be calculated. Cumulative rate of subjects for reference periods (summary of cycles 2-4, 5-7, 8-10 and 11-13) will be provided. Cumulative rates only for reference periods will also be presented for number and percent of subjects with prolonged bleeding and spotting $>$ nine days/ $>$ 14 days and the number of bleeding and spotting episodes.

Number and percent of days per cycle and reference period with bleeding and spotting, scheduled bleeding, scheduled spotting and unscheduled bleeding, unscheduled spotting and duration of scheduled bleeding, scheduled spotting, unscheduled bleeding and unscheduled spotting will be analyzed descriptively.

IMP acceptability will be summarized by default frequency tabulation. Shift tables will be provided to illustrate change from V3 to V6/EDV. Additionally for subjects who switched from another oral contraceptive to the IMP default frequency tables will be summarized to present change of subject wellbeing.

Pharmacokinetics analyses of LF111 will be conducted using a population pharmacokinetic method to determine individual estimates of LF111 pharmacokinetic parameters. In addition, a model-based covariate analysis will be performed to explore the effect of pre-defined covariates, including body weight/body mass index, on the apparent clearance of DRSP, and the influence of any significant covariates on the exposure over the dose interval assessed.

Sample size calculation:

At least 920 subjects will be allocated to treatment to have at least 5000 evaluable cycles for the PI calculation in non-breastfeeding women aged ≤ 35 years (at the time of trial enrollment). Additionally, a minimum of 75 subjects aged > 35 years will be allocated to treatment. The calculations are based on empirical values including firstly a rate of 24.8% of subjects using back-up contraception or not having intercourse. Secondly, 45% of subjects are assumed to drop out of the trial. The prime target is to collect at least 5000 evaluable cycles.