



## Clinical trial results:

**A study to evaluate the effect on the endometrium of a new formulation containing 4 mg drospirenone (Drospirenone 4 mg film-coated tablet) administered over a period of 13 cycles. A monocentric, open, multiple dose trial in healthy female subjects at risk of pregnancy**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-002300-13 |
| Trial protocol           | BG             |
| Global end of trial date | 20 April 2015  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 19 June 2020 |
| First version publication date | 19 June 2020 |

### Trial information

#### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | CCR13001,CF111/205 |
|-----------------------|--------------------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Laboratorios León Farma S.A.   |
| Sponsor organisation address | La Vallina s/n, Polígono Industrial de Navatejera, León, Spain, 24008              |
| Public contact               | Chief Scientific Officer, Enrico Colli, +34 91 771 15 00, enrico.colli@exeltis.com |
| Scientific contact           | Chief Scientific Officer, Enrico Colli, +34 91 771 15 00, enrico.colli@exeltis.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 23 June 2015  |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 20 April 2015 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To assess the endometrial safety of an oral test preparation containing 4 mg drospirenone (Test IMP: Drospirenone 4 mg film-coated tablet) after multiple dose administration of 4 mg drospirenone for a total duration of 13 cycles of 28 days each: 24 days of active treatment followed by 4 days placebo treatment per treatment cycle.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 30 November 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Bulgaria: 22 |
| Worldwide total number of subjects   | 22           |
| EEA total number of subjects         | 22           |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 22 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Healthy woman at risk of pregnancy, Age between 18 and 40 years, At least four menstrual cycles during the last six months before screening were regular, At least one regular menstrual cycle after the end of prev intake of oral contraceptive, Systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg, in sitting position, after 5 min rest

### Pre-assignment

Screening details:

Screening period of about 8 weeks. The subjects underwent a clinical, gynecological, and laboratory screening examination with the aim of evaluating their eligibility for the trial. As soon as all results were available, the eligible subjects started treatment with the test product on the first day of bleeding in the following menstrual cycle.

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment Period (overall period) |
| Is this the baseline period? | Yes                               |
| Allocation method            | Not applicable                    |
| Blinding used                | Not blinded                       |

Blinding implementation details:

Not blinded study

### Arms

|  |                                       |
|--|---------------------------------------|
| Arm title                              | Treatment Arm                         |
| Arm description: -                     |                                       |
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Drospirenone 4 mg film-coated tablets |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Tablet                                |
| Routes of administration               | Oral use                              |

Dosage and administration details:

4 mg drospirenone per film-coated tablet, 1 film-coated tablet (=4 mg drospirenone) as a multiple dose of one tablet per day for a total duration of 13 cycles of 28 days each: 24 days of active treatment followed by 4 days placebo treatment per cycle

| Number of subjects in period 1 | Treatment Arm |
|--------------------------------|---------------|
| Started                        | 22            |
| Completed                      | 17            |
| Not completed                  | 5             |
| Consent withdrawn by subject   | 2             |
| Adverse event, non-fatal       | 1             |
| Loss of contact                | 1             |
| Loss of contact after visit 2  | 1             |



## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Treatment Arm |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values                | Treatment Arm | Total |  |
|---------------------------------------|---------------|-------|--|
| Number of subjects                    | 22            | 22    |  |
| Age categorical<br>Units: Subjects    |               |       |  |
| Adults 18 - 40 years                  | 22            | 22    |  |
| Gender categorical<br>Units: Subjects |               |       |  |
| Female                                | 22            | 22    |  |

### Subject analysis sets

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | Safety population set |
|----------------------------|-----------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

A total number of 21 healthy pre-menopausal female subjects were confirmed to have started the treatment with study medication

| Reporting group values                | Safety population set |  |  |
|---------------------------------------|-----------------------|--|--|
| Number of subjects                    | 21                    |  |  |
| Age categorical<br>Units: Subjects    |                       |  |  |
| Adults 18 - 40 years                  | 21                    |  |  |
| Gender categorical<br>Units: Subjects |                       |  |  |
| Female                                | 21                    |  |  |

## End points

### End points reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Treatment Arm         |
| Reporting group description: -   |                       |
| Subject analysis set title   | Safety population set |
| Subject analysis set type  | Safety analysis       |
| Subject analysis set description:  |                       |
| A total number of 21 healthy pre-menopausal female subjects were confirmed to have started the treatment with study medication |                       |

### Primary: Rating of endometrial biopsy

|  |   |
|--|---|
| End point title  | Rating of endometrial biopsy <sup>[1]</sup> |
| End point description:   |   |
| The endometrial biopsy was taken by means of Pipelle® Endometrial Suction Curette and evaluated by a local independent pathologist. The endometrial samples were examined microscopically and the histological result was documented in the CRF at visit 2. The endometrial biopsy result was classified in 6 categories (according to Lindgren et al., 19921): Inadequate, Atrophic, Proliferative, Secretory, Hyperplasia and Non-secretory. |   |
| End point type   | Primary                                     |
| End point timeframe:   |   |
| Visit 1 and Visit 7  |   |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: this is not a comparative study. Statistical analyses were not performed

| End point values            | Treatment Arm   | Safety population set |  |  |
|-----------------------------|-----------------|-----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set  |  |  |
| Number of subjects analysed | 21              | 21                    |  |  |
| Units: category             |                 |                       |  |  |
| Inadequate                  | 4               | 4                     |  |  |
| Atrophic                    | 0               | 0                     |  |  |
| Proliferative               | 12              | 12                    |  |  |
| Secretory                   | 3               | 3                     |  |  |
| Hyperplasia                 | 0               | 0                     |  |  |
| Non-secretory               | 0               | 0                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Endometrial thickness

|   |                       |
|---|-----------------------|
| End point title   | Endometrial thickness |
| End point description:  |                       |
| End point type  | Secondary             |
| End point timeframe:  |                       |
| The endometrial thickness was measured by means of transvaginal sonography during the gynecological |                       |

| End point values            | Treatment Arm   | Safety population set |  |  |
|-----------------------------|-----------------|-----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set  |  |  |
| Number of subjects analysed | 22              | 21                    |  |  |
| Units: mm                   | 21              | 21                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of adverse events and serious adverse events

|   |  |
|---|--|
| End point title                                     | Incidence of adverse events and serious adverse events |
| End point description:                              |  |
| End point type                                      | Secondary  |
| End point timeframe:<br>during the treatment period |  |

| End point values            | Safety population set |  |  |  |
|-----------------------------|-----------------------|--|--|--|
| Subject group type          | Subject analysis set  |  |  |  |
| Number of subjects analysed | 21                    |  |  |  |
| Units: number of AEs        | 21                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: changes from baseline in the results of clinical examination and vital

|   |  |
|---|--|
| End point title   | changes from baseline in the results of clinical examination and vital |
| End point description:  |  |
| End point type  | Secondary  |
| End point timeframe:<br>general state (visit 1 and visit 8), physical examination (visit 1 and visit 8), body temperature (visit 1), heart rate, systolic and diastolic blood pressure (visit 1 to visit 8) |  |

|                             |                       |  |  |  |
|-----------------------------|-----------------------|--|--|--|
| <b>End point values</b>     | Safety population set |  |  |  |
| Subject group type          | Subject analysis set  |  |  |  |
| Number of subjects analysed | 21                    |  |  |  |
| Units: various              | 21                    |  |  |  |

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:  
during treatment

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Safety Set |
|-----------------------|------------|

Reporting group description: -

| Serious adverse events  | Safety Set     |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events                   |                |  |  |
| subjects affected / exposed   | 2 / 21 (9.52%) |  |  |
| number of deaths (all causes)                                       | 0              |  |  |
| number of deaths resulting from adverse events                      | 0              |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |  |  |
| Uterine leiomyoma   |                |  |  |
| subjects affected / exposed   | 1 / 21 (4.76%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Renal and urinary disorders   |                |  |  |
| Hydronephrosis  |                |  |  |
| subjects affected / exposed   | 1 / 21 (4.76%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Hydroureter   |                |  |  |
| subjects affected / exposed   | 1 / 21 (4.76%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |
| Calculus urethral   |                |  |  |
| subjects affected / exposed   | 1 / 21 (4.76%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1          |  |  |
| deaths causally related to treatment / all                          | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Renal colic                                     |                |  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Pyelonephritis chronic                          |                |  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Safety Set       |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 11 / 21 (52.38%) |  |  |
| Investigations  |                  |  |  |
| Hepatic enzyme increased                              |                  |  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Weight increased                                      |                  |  |  |
| subjects affected / exposed                           | 2 / 21 (9.52%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Injury, poisoning and procedural complications        |                  |  |  |
| Hand fracture   |                  |  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Wrist fracture  |                  |  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Surgical and medical procedures                       |                  |  |  |
| Tooth extraction                                      |                  |  |  |
| subjects affected / exposed                           | 1 / 21 (4.76%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Nervous system disorders                              |                  |  |  |
| Headache  |                  |  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 21 (9.52%)<br>2   |  |  |
| General disorders and administration<br>site conditions<br>Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 21 (4.76%)<br>1   |  |  |
| Reproductive system and breast<br>disorders<br>Uterine polyp<br>subjects affected / exposed<br>occurrences (all)   | 1 / 21 (4.76%)<br>1   |  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 1 / 21 (4.76%)<br>1   |  |  |
| Psychiatric disorders<br>Alcoholic hangover<br>subjects affected / exposed<br>occurrences (all)  | 1 / 21 (4.76%)<br>1   |  |  |
| Musculoskeletal and connective tissue<br>disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 21 (4.76%)<br>1   |  |  |
| Infections and infestations<br>Acute sinusitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Cystitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyelonephritis chronic<br>subjects affected / exposed<br>occurrences (all)<br><br>Vaginal infection | 1 / 21 (4.76%)<br>1<br><br>1 / 21 (4.76%)<br>1<br><br>1 / 21 (4.76%)<br>1<br><br>1 / 21 (4.76%)<br>1<br><br>1 / 21 (4.76%)<br>1 |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 21 (9.52%) |  |  |
| occurrences (all)           | 2              |  |  |
| Viral infection             |                |  |  |
| subjects affected / exposed | 1 / 21 (4.76%) |  |  |
| occurrences (all)           | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 17 December 2013 | substantial Amendment 1.0 to the study protocol (Final Version 1.0 from 08-Jul-2013), related to corrections in the inclusion criteria, to additional exclusion/withdrawal criteria and additional information to the Subject Information and Informed Consent, was issued on 17-Oct-2013 on regulatory authority (Bulgarian Drug Agency) request |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported