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
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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 Units: Subjects			
Adults 18 - 40 years	22	22	
Gender categorical 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 Units: Subjects			
Adults 18 - 40 years	21		
Gender categorical 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[1]

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:

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:

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)

End point values	Safety population set			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: various	21			

Statistical analyses

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 %

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

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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported