Clinical trial results:
Open-Label, Randomized Study to Evaluate the Influence on the Hormonal and Ovarian Activity of Two Different Dosages of Drospirenone (either 4.0 mg for 24 Days or 2.8 mg Daily for 28 Days) Over Two Treatment Cycles in 50 Healthy, Young Females

Summary

EudraCT number	2011-004085-15
Trial protocol	DE
Global end of trial date	10 April 2012

Results information

Result version number	v1 (current)
This version publication date	29 May 2020
First version publication date	29 May 2020

Trial information

Trial identification

Sponsor protocol code	CF111/203

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, Chemo Research, 0034 917711500, enrico.colli@exeltis.com
Scientific contact	Chief Scientific Officer, Chemo Research, 0034 917711500, 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	12 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the ovulation inhibition potential reflected by the hormonal and ovarian activity of two different dosages and intake regimens of drospirenone (DRSP) in 50 healthy women.
Subjects will be assigned to one of two treatment regimens after stratification for the ovulation day in the precycle.

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator: -

Actual start date of recruitment	01 October 2011
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	Germany: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	53
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy premenopausal females of any ethnic origin (18 to 35 years of age), inclusive; (smokers not older than 30 years; smokers ≤ 30 years up to 10 cigarettes daily), BMI of 18-30 kg/m2, history of regular cycles, blood pressure after resting for 5 minutes between 90-140 mmHg (systolic) and 50-90 mmHg (diastolic), etc.

Pre-assignment

Screening details:

Screening was divided in two sections: The first section took place before the start of the precycle and the second part followed after an
ovulation could be detected in the precycle.

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 applicable, because this was an open-label trial.

Arms

Arm title	Treatment Arm

Arm description:

Fifty subjects were allocated either to Treatment 1 (4.0 mg DRSP for 24 days followed by 4 placebo tablets) or Treatment 2 (2.8 mg DRSP for 28 days) over two treatment cycles.

Arm type	Experimental
Investigational medicinal product name	Drospirenone 4.0 mg coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

28 coated tablets, oral, once daily,

Investigational medicinal product name	Drospirenone 2.8 mg coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

28 tablets, oral, once daily

Number of subjects in period 1	Treatment Arm
Started	53
Completed	50
Not completed	3
Consent withdrawn by subject	1

Intake of prohibited medication	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Arm

Reporting group description:

Fifty subjects were allocated either to Treatment 1 (4.0 mg DRSP for 24 days followed by 4 placebo tablets) or Treatment 2 (2.8 mg DRSP for 28 days) over two treatment cycles.

Reporting group values	Treatment Arm	Total	
Number of subjects	53	53	
Age categorical Units: Subjects			
Adults (18 to 35 years)	53	53	
Gender categorical Units: Subjects			
Female	53	53	

Subject analysis sets

Subject analysis set title	Per Protoco Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

Consisted of all subjects from the FAS, excluding volunteers with major protocol deviations

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) consisted of all subjects who had received at least one dose of the product (Treatment 1 or Treatment 2), for whom CRF entries were available, and for whom at least one Hoogland-Score result was available after start of treatment, regardless of protocol deviations

Subject analysis set title	Safety Analysis Set (SF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety analysis set (SF) consisted of all volunteers who had received at least one dose of investigational product

Reporting group values	Per Protoco Set (PPS)	Full Analysis Set (FAS)	Safety Analysis Set (SF)
Number of subjects	49	50	52
Age categorical Units: Subjects			
Adults (18 to 35 years)	49	50	52
Gender categorical Units: Subjects			
Female	49	50	52

End points

End points reporting groups

Reporting group title	Treatment Arm
Reporting group description:	
Fifty subjects were allocated either to Treatment 1 (4.0 mg DRSP for 24 days followed by 4 placebo tablets) or Treatment 2 (2.8 mg DRSP for 28 days) over two treatment cycles.	
Subject analysis set title	Per Protoco Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Consisted of all subjects from the FAS, excluding volunteers with major protocol deviations	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) consisted of all subjects who had received at least one dose of the product (Treatment 1 or Treatment 2), for whom CRF entries were available, and for whom at least one Hoogland-Score result was available after start of treatment, regardless of protocol deviations	
Subject analysis set title	Safety Analysis Set (SF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety analysis set (SF) consisted of all volunteers who had received at least one dose of investigational product	

Primary: Hoogland score

End point title	Hoogland score[1]
End point description:	
The Hoogland Score is a composite parameter of follicle size as well as estradiol and progesterone levels	
End point type	Primary
End point timeframe:	
1st cycle: day 3, 6, 9, 12, 15, 18, 21, 24, 27 2nd cycle: day 3, 6, 9, 12, 15, 18, 21, 24, 27	

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: statistical analyses have not been performed

End point values	Treatment Arm	Per Protoco Set (PPS)	Full Analysis Set (FAS)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	49	50	
Units: number	53	49	50	

Statistical analyses

No statistical analyses for this end point

Secondary: LH and FSH

End point title	LH and FSH
End point description:	
The pituitary hormones LH and FSH were determined to interpret the influence of the IMP on the central	

hormonal regulation and feedback

End point type	Secondary

End point timeframe:

Follicle phase, ovulatory phase, luteal phase

End point values	Treatment Arm	Per Protoco Set (PPS)	Full Analysis Set (FAS)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	49	50	
Units: U/L	53	49	50	

Statistical analyses

No statistical analyses for this end point

Secondary: Endometrial thickness

End point title	Endometrial thickness

End point description:

Endometrial thickness was assessed in order to determine any changes in the endometrial bed which are inappropriate for nidation. Especially in case of any occurring ovulation under treatment the corresponding endometrium thickness was evaluated and compared to the ovulatory precycle. A thickness of < 6 mm was regarded as non-conceptional endometrium

End point type	Secondary

End point timeframe:

It was measured at each visit

End point values	Treatment Arm	Per Protoco Set (PPS)	Full Analysis Set (FAS)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	49	50	
Units: mm	53	49	50	

Statistical analyses

No statistical analyses for this end point

Secondary: bleeding pattern

End point title	bleeding pattern

End point description:

Evaluation of bleeding intensities was based on the following classification, whereas the subjects were informed not to consider the change of any tampons or sanitary napkins for hygienic reasons or well-being:
Spotting: very mild bleeding

Slight: bleeding requiring the use of 1-2 tampons or sanitary napkins per day
Moderate: bleeding requiring the use of 3-4 tampons or sanitary napkins per day
Heavy: bleeding requiring the use of 5 or more tampons or sanitary napkins per day.

End point type	Secondary

End point timeframe:

daily diary entries by the subjects

End point values	Treatment Arm	Per Protoco Set (PPS)	Full Analysis Set (FAS)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	49	50	
Units: intensity	53	49	50	

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

Adverse events (AE) were all disturbances to health and well-being, subjective and objective disease symptoms (including pathological, clinically relevant changes in laboratory values), intercurrent illnesses and accidents observed during the course of a clinical trial, independent of whether a causal relationship with the administration of the investigational drug was possible.

End point type	Secondary

End point timeframe:

An AE which was reported spontaneously by the subject or which was observed by the clinical investigator was to be monitored during the clinical trial or registered at each visit and entered into the CRF adverse event page.

End point values	Treatment Arm	Safety Analysis Set (SF)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	53	52		
Units: number of AEs	53	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Laboratory Evaluations

End point title	Clinical Laboratory Evaluations

End point description:

Haematology: Leucocytes, erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV),

mean corpuscular haemoglobin (MCH), platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes
Liver function: Glutamate pyruvate transaminase (ALAT/GPT), glutamate oxaloacetate transaminase (ASAT/GOT)
Serum chemistry: Sodium, potassium, chloride, creatinine
Virology: HbsAg, anti-HCV, anti-HIV
Urinalysis: glucose, ß-hCG (at the trial site and home test)

End point type	Secondary

End point timeframe:

virology only once at screening; Safety blood sampling was conducted under at least 4 hours fasting conditions. Subjects were requested to keep a fasting period prior to their visit (e.g. without breakfast).

End point values	Treatment Arm	Safety Analysis Set (SF)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	53	52		
Units: N/A	53	52		

Statistical analyses

No statistical analyses for this end point

Secondary: vital signs

End point title	vital signs

End point description:

Vital signs parameters comprised systolic blood pressure, diastolic blood pressure, heart rate, and body mass index (BMI)

End point type	Secondary

End point timeframe:

at screening and final examination

End point values	Treatment Arm	Safety Analysis Set (SF)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	53	52		
Units: N/A	53	52		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: during the course of the clinical trial	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	Treatment group DRSP 4 mg
Reporting group description: -	
Reporting group title	Treatment group DRSP 2.8 mg
Reporting group description: subjects taking drospirenone 2.8 mg	

Serious adverse events	Treatment group DRSP 4 mg	Treatment group DRSP 2.8 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment group DRSP 4 mg	Treatment group DRSP 2.8 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 27 (77.78%)	24 / 25 (96.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 27 (18.52%)	8 / 25 (32.00%)	
occurrences (all)	21	16	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 27 (11.11%)	4 / 25 (16.00%)	
occurrences (all)	7	4	
Ovarian cyst			

subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	4	3	
Breast discomfort			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 27 (14.81%)	1 / 25 (4.00%)	
occurrences (all)	5	1	
Abdominal pain lower			
subjects affected / exposed	2 / 27 (7.41%)	2 / 25 (8.00%)	
occurrences (all)	4	2	
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 27 (14.81%)	2 / 25 (8.00%)	
occurrences (all)	6	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 27 (18.52%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	2 / 27 (7.41%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 27 (40.74%)	17 / 25 (68.00%)	
occurrences (all)	13	20	
Oral herpes			

subjects affected / exposed	3 / 27 (11.11%)	5 / 25 (20.00%)	
occurrences (all)	8	5	
Cystitis			
subjects affected / exposed	3 / 27 (11.11%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported