Clinical trial results:
A Pivotal, Multicenter, Non-Comparative Trial on the Contraceptive Efficacy, Safety and Tolerability of Drospirenone as LF111 During 13 Cycles

Summary

EudraCT number	2010-021787-15
Trial protocol	DE HU CZ RO
Global end of trial date	18 February 2013

Results information

Result version number	v1 (current)
This version publication date	12 October 2019
First version publication date	12 October 2019

Trial information

Trial identification

Sponsor protocol code	CF111/301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Chemo France
Sponsor organisation address	7 rue Victor Hugo, Sevres, France, 92310
Public contact	Enrico Colli, Chemo Research, 0034 91 302 15 00, enrico.colli@exeltis.com
Scientific contact	Enrico Colli, Chemo Research, 0034 91 302 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	18 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the contraceptive efficacy of LF111

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	11 July 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	Poland: 199
Country: Number of subjects enrolled	Romania: 119
Country: Number of subjects enrolled	Czech Republic: 178
Country: Number of subjects enrolled	Germany: 158
Country: Number of subjects enrolled	Hungary: 70
Worldwide total number of subjects	724
EEA total number of subjects	724

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)	724

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 824 subjects were screened, 100 subjects were screening failures and 724 subjects were allocated to treatment (ATS). Of these 724 subjects, 11 prematurely terminated the trial before the start of treatment due to withdrawal of consent (5 subjects), ineligibility (3 subjects), other reasons (2 subjects) and pregnancy (1 subject).

Pre-assignment

Screening details:

Healthy woman at risk of pregnancy, at the age of 18-45 y. For Germany: Woman without uncontrolled current diseases at risk of pregnancy, at the age of 18-45 y. For starters: At least 4 menstrual cycles during the last 6 m before Visit 1 were regular (i.e. cycle length between 24 and 35 days). Systolic BP<140 mmHg, diastolic BP<90 mmHg.

Period 1

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

Blinding implementation details:

N/A

Arms

Arm title	experimental

Arm description:

Single arm

Arm type	Experimental
Investigational medicinal product name	Drospirenone 4 mg film-coated tablets
Investigational medicinal product code	LF111
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

In this trial each subject received one tablet of IMP per day. During the medication cycle the subjects were to take 24 active tablets (each containing 4 mg DRSP) followed by four placebo tablets.

Number of subjects in period 1	experimental
Started	724
Completed	515
Not completed	209
Physician decision	1
wish of pregnancy	2
subject refused ediary	1
Ineligibility	7
Lost of follow up	16
Family reasons	1

intake termination by subject´s mistake	1
non compliance of the subject	3
Consent withdrawn by subject	83
Adverse event, non-fatal	88
problems with e-diary	1
Pregnancy	3
BMI > 30	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	724	724	
Age categorical Units: Subjects			
Adults (18-64 years)	724	724	
Gender categorical Units: Subjects			
Female	724	724	

Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set (SS) consisted of all subjects who had received at least one dose of IMP

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) consists of all subjects who:
- are included in the SS (took at least one dose of IMP)
- who were not pregnant at the date of first IMP intake.
The full analysis set will be used for efficacy analysis.

Reporting group values	Safety Set	Full analysis set	
Number of subjects	713	713	
Age categorical Units: Subjects			
Adults (18-64 years)	713	713	
Gender categorical Units: Subjects			
Female	713	713	

End points

End points reporting groups

Reporting group title	experimental
Reporting group description:	
Single arm	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set (SS) consisted of all subjects who had received at least one dose of IMP	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) consists of all subjects who: - are included in the SS (took at least one dose of IMP) - who were not pregnant at the date of first IMP intake. The full analysis set will be used for efficacy analysis.	

Primary: Overall Pearl Index

End point title	Overall Pearl Index[1]
End point description:	
Overall PI = number of pregnancies*1300/number of medication cycles Overall PI was to include all pregnancies which occurred during the study. Pregnancies following premature termination of IMP were to be excluded from calculations unless intravaginal ultrasound examination and β–HCG test was not performed to determine whether the date of conception was after the premature discontinuation. Medication cycle was defined as 28 days starting with the administration of the first tablet from the blister containing 28 tablets and ending with the last day of intake	
End point type	Primary
End point timeframe:	
PI is calculated at the end of the study	

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 a single arm, open label study. Thus, a comparison to a reference product is not planned

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: Pearl Index (PI) for method failures

End point title	Pearl Index (PI) for method failures
End point description:	
Method failure PI = number of pregnancies (M) * 1300/number of perfect medication cycles. Method failure was to include all pregnancies categorised as M. M=pregnancy where the subject was compliant	

with IMP dosing near the time of conception and estimated date of conception was during treatment period (extended with a maximum of 2 days).

End point type	Secondary

End point timeframe:

At the end of the study

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: PI after correction for additional contraception and for sexual activitis status

End point title	PI after correction for additional contraception and for sexual activitis status

End point description:

PI after correction for additional contraception and for sexual activity status = number of pregnancies (M,U) * 1300/exposure cycles excluding those with back-up contraception and without sexual activity.
M (method failure) = pregnancy where the subject was compliant with IMP dosing near the time of conception and estimated date of conception was during treatment period (extended with a maximum of 2 days).
U (user failure) = pregnancy where the subject failed to comply with IMP dosing near the time of conception and estimated date of conception was during treatment period (extended with a maximum of 2 days).

End point type	Secondary

End point timeframe:

At the end of the study

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

Adverse events (AEs) will be reported on a per-subject basis. This implies that even if a subject reported the same event repeatedly, the event will be counted only once. In the latter case, the event will be assigned the worst severity and strongest relationship to the IMP. The presentation of AEs is therefore restricted to the incidence per subject of AEs assigned to the Treatment or Follow-up Period.
Treatment-emergent adverse events (TEAEs) were defined as AEs which started at or after the first administration of the IMP and included those events started prior to the first administration of the IMP but which worsened after the first intake. AEs starting after the last
administration of the IMP but within the follow-up period were also regarded as treatment emergent.
TEAEs leading to trial termination were obtained from the AE form, where the field "Action taken on study drug" was indicated as "drug withdrawn".

End point type	Secondary

End point timeframe:

Anytime during the study

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Laboratory Evaluation

End point title	Clinical Laboratory Evaluation

End point description:

Haematology: Haemoglobin, red blood cell count, mean corpuscular volume (M.C.V.) and associated parameters , haematocrit, M.C.H., white blood cell count, differential white blood cell count including neutrophils, lymphocytes, eosinophils, basophils and monocytes, platelet count
Biochemistry: Sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), calcium, glucose, total proteins, albumin, total cholesterol (HDL, LDL cholesterol), triglycerides, gamma glutamyl transferase, total and direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH)
Urinalysis Leukocytes, nitrite, protein, glucose, ketones, blood, pH, urobilinogen, bilirubin, haemoglobin

End point type	Secondary

End point timeframe:

Blood samples for haematology, biochemistry and thyroid function assessments and urine samples for urinalysis will be collected at V1a, V3, V4, V5 (electrolytes only), and V6 (or EDV).A dipstick will be used for urinalysis at V1a, V4 and V6 (or EDV)

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: vital signs

End point title	vital signs

End point description:

Body weight and body mass index, Blood pressure and heart rate

End point type	Secondary

End point timeframe:

Body weight, blood pressure and heart rate were measured at screening, V4 and V6 (EDV).

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability

End point title	Tolerability

End point description:

Number and rate of subjects with different bleeding patterns will be presented for each cycle or reference period. The Clopper-Pearson 95% confidence interval for rate of subjects will be calculated. Cumulative rate of subjects with different bleeding patterns for reference periods will be provided.

End point type	Secondary

End point timeframe:

From Day 1 of Medication Cycle 1 (i.e. start of IMP intake) to V6/EDV, subjects will record any vaginal bleeding in their electronic diary.

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Secondary: IMP acceptablitity

End point title	IMP acceptablitity

End point description:

- How did you tolerate the intake of the trial medication (excellent, good, moderate, bad, no answer)
- How was your wellbeing during the intake of the trial medication (excellent, good, moderate, bad, no answer)
- Did the subject switch from another oral contraceptive to the study medication? (yes, no)
- If yes: How was your wellbeing during the intake of the trial medication in comparison to the time when you took your former oral contraceptive, for switchers from another oral contraceptive only (better, unchanged, worse, no answer)
- Acceptability of the IMP from the physician’s point of view (excellent, good, moderate, bad, no answer)

End point type	Secondary

End point timeframe:

At V2 to V6/EDV, the subject will be asked by the investigator for an assessment regarding IMP acceptability

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	713			
Units: N/A	713			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs which started at or after the first administration of the IMP and included those events started prior to the first administration of the IMP but which worsened after the first intake. AEs starting after last adm of the IMP but within the FU period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

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	9 / 117 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Breast prosthesis implantation			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Facet joint syndrome			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salpingo-oophoritis			
subjects affected / exposed	1 / 117 (0.85%)		
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	108 / 117 (92.31%)		

Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	15 / 117 (12.82%)		
occurrences (all)	15		
Weight increased			
subjects affected / exposed	12 / 117 (10.26%)		
occurrences (all)	12		
Nervous system disorders			
Headache			
subjects affected / exposed	32 / 117 (27.35%)		
occurrences (all)	44		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	19 / 117 (16.24%)		
occurrences (all)	22		
Menstruation irregular			
subjects affected / exposed	15 / 117 (12.82%)		
occurrences (all)	17		
Cervical dysplasia			
subjects affected / exposed	14 / 117 (11.97%)		
occurrences (all)	14		
Vaginal haemorrhage			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	10		
Breast pain			
subjects affected / exposed	8 / 117 (6.84%)		
occurrences (all)	9		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	11		
Abdominal pain			
subjects affected / exposed	9 / 117 (7.69%)		
occurrences (all)	10		
Diarrhoea			

subjects affected / exposed occurrences (all)	8 / 117 (6.84%) 10		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 45 / 117 (38.46%) 47 10 / 117 (8.55%) 11		
Psychiatric disorders Libido decreased subjects affected / exposed occurrences (all)	 12 / 117 (10.26%) 12		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Vulvovaginal mycotic infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Vaginal infection subjects affected / exposed occurrences (all) Pharyngitis	 22 / 117 (18.80%) 25 21 / 117 (17.95%) 23 19 / 117 (16.24%) 20 13 / 117 (11.11%) 17 13 / 117 (11.11%) 16 12 / 117 (10.26%) 15 12 / 117 (10.26%) 13 		

subjects affected / exposed	8 / 117 (6.84%)		
occurrences (all)	9		
Sinusitis			
subjects affected / exposed	8 / 117 (6.84%)		
occurrences (all)	8		
Vulvovaginal candidiasis			
subjects affected / exposed	8 / 117 (6.84%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2011	This protocol amendment was prepared not to exclude women with a BMI > 30 kg/m2; to correct an error regarding drug accountability in the protocol; to correct the inconsistency in urinalysis laboratory parameters and to correct the inconsistency between the CRF and the protocol with respect to IMP acceptability answer options.
30 June 2011	With this protocol amendment the permitted delay in DRSP intake was extended from 12 to 24 hours, based on the preliminary results of the pilot study CF111/201A. Sexual activity for each medication cycle had to be confirmed in the e-diary; Visit 6 was scheduled for Day 29+2 of the 13th medication cycle to ensure that e-diaries with complete data for the 13th medication cycle could be collected and final drug accountabilitycould be performed at Visit 6.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported