Clinical trial results:
Multicentre, Open-Label Trial to Assess the Safety and Tolerability of LF111 (Drospirenone 4.0 mg) Over 6 Cycles in Female Adolescents, With a 7-Cycle Extension Phase

Summary

EudraCT number	2013-005234-37
Trial protocol	DE NL FI SE
Global end of trial date	19 September 2016

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	CF111/304

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	Project Leader, CHEMO France, 0034 917711500, laura.ullate@exeltis.com
Scientific contact	Project Leader, CHEMO France, 0034 917711500, laura.ullate@exeltis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001495-PIP01-13
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	19 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate safety and tolerability including bleeding pattern.

Protection of trial subjects:

Due to the vulnerability of adolescents and absence of marketing authorization for LF111, an Independent Data Monitoring Committee (IDMC) was constituted.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Ukraine: 40
Worldwide total number of subjects	103
EEA total number of subjects	63

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)	103
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Following the national legislations, the lower age limit in Germany was 14 years, in Sweden 15 years and in Ukraine 16 years. In Finland, based on the trial centre's decision, it was 15 years, because parental consent was not needed at this age. It was planned to screen about 130 subjects to have approximately 100 subjects evaluable for safety.

Pre-assignment

Screening details:

Inclusion criteria: female adolescents aged 12-17 years, with or without intact hymen; postmenarcheal for at least six months; starters of oral contraceptives with at least four regular menstrual cycles during the last six months before screening. Eight subjects were screening failures.

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:

out of the 103 subjects who started the trial, 85 subjects entered the extension phase and 74 subjects completed the extension phase and overall trial (11 subjects prematurely terminated the extension phase)

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

Dosage and administration details:

Blister package with 28 LF111 coated tablets (24 white tablets containing 4.0 mg drospirenone, 4 green placebo tablets), oral administration once daily. Duration of the treatment.: 7 cycles x 28 days = 196 days (extension phase)

Number of subjects in period 1	experimental
Started	103
Completed	74
Not completed	29
Consent withdrawn by subject	4
withdrawal of consent	1
Adverse event, non-fatal	12
not continuing the extension phase	4
Non-compliance	2

IMP gap	1
Lost to follow-up	3
Protocol deviation	1
Moved abroad	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	103	103	
Age categorical Units: Subjects			
Adolescents (12-17 years)	103	103	
Gender categorical Units: Subjects			
Female	103	103	

Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Per protocol

Subject analysis set description:

A total of 103 subjects were allocated to treatment with DRSP 4.0 mg, of these 102 subjects received at least one dose of IMP and were included in the Safety Set.

Subject analysis set title	Core Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Core Per Protocol Set (CPPS), defined in the core phase DRM consisted of all subjects who were included in the SS and did not present any major protocol deviation during the core phase of the trial.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set consisted of all subjects who were included in the SS and did not present any major protocol deviation

Reporting group values	Safety Set	Core Per Protocol Set	Per Protocol Set
Number of subjects	102	93	87
Age categorical Units: Subjects			
Adolescents (12-17 years)	102		
Gender categorical Units: Subjects			
Female	102		

End points

End points reporting groups

Reporting group title	experimental

Reporting group description:

out of the 103 subjects who started the trial, 85 subjects entered the extension phase and 74 subjects completed the extension phase and overall trial (11 subjects prematurely terminated the extension phase)

Subject analysis set title	Safety Set
Subject analysis set type	Per protocol

Subject analysis set description:

A total of 103 subjects were allocated to treatment with DRSP 4.0 mg, of these 102 subjects received at least one dose of IMP and were included in the Safety Set.

Subject analysis set title	Core Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Core Per Protocol Set (CPPS), defined in the core phase DRM consisted of all subjects who were included in the SS and did not present any major protocol deviation during the core phase of the trial.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set consisted of all subjects who were included in the SS and did not present any major protocol deviation

Primary: Assessment of bleeding pattern over the 6 months of the core study

End point title	Assessment of bleeding pattern over the 6 months of the core study[1]

End point description:

Analysis of the vaginal bleeding pattern included:
- Number and rate of subjects with different bleeding patterns, with bleeding and /or spotting, separately for bleeding and spotting, including bleeding by intensity were to be presented for each day of treatment in the corresponding cycle, for each treatment cycle and cumulatively by reference period (Cycles 2 to 4 and Cycles 2 to 6).
- Number of bleeding and/or spotting days, separately for bleeding and spotting, and numbers of days with bleeding by intensity were to be summarised by means of the default summary statistics for each treatment cycle and by reference period. Scheduled and unscheduled bleeding presented separately.
-Correlation between incidence of unscheduled bleeding and/or spotting and number of missing tablets or entries. Default summary statistics for missed tablets or diary entries by treatment cycle and reference period. p-values from the Wilcoxon-rank-sum-test are presented

End point type	Primary

End point timeframe:

6 cycles

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	experimental	Safety Set	Core Per Protocol Set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	102	93	
Units: number of subjects	103	102	93	

Statistical analyses

No statistical analyses for this end point

Primary: Withdrawal due to TEAEs based on abnormal bleeding in the core phase

End point title	Withdrawal due to TEAEs based on abnormal bleeding in the core phase[2]

End point description:

The number of subjects with at least one TEAE leading to premature discontinuation based on abnormal bleeding in the core phase will be analysed descriptively for the safety set.

End point type	Primary

End point timeframe:

during the 6 cycles core phase

Notes:

[2] - 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	experimental	Safety Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	103	102		
Units: number of subjects	103	102		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

A detailed description of each adverse event (AE) includes:
- Adverse Event
- The start and stop date of the adverse event or "ongoing"
- Severity (mild, moderate, severe)
- Relationship to the IMP (not related, unlikely related, possibly related, related)
- Frequency (single, intermittent, continuous)
- Action taken on trial treatment (dose not changed, drug interrupted, drug withdrawn, unknown, not applicable)
- Other actions (none, medication required, tests required, hospitalisation required or prolonged, other)
- Outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown)
- Serious (yes, no)

End point type	Secondary

End point timeframe:

anytime during the 13 months trial, including extension phase

End point values	experimental	Safety Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	102	102		
Units: number of AEs	102	102		

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 (MCV) and associated parameters, haematocrit, MCH, 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), Thyroid function (TSH)
Urinalysis: Leukocytes, nitrite, protein, glucose, ketones, blood, pH, urobilinogen, bilirubin, haemoglobin (dipstick test).
Pregnancy test: Urine human chorionic gonadotropin (HCG) test

End point type	Secondary

End point timeframe:

Blood samples and urine samples taken at Visit 1a,Visit 6/EDV and at Visit 8/EDV.
Clinical laboratory variables summarised at Visit 1a,Visit 6/EDV and at Visit 8/EDV.
Urine pregnancy test at V1a, V1b, V2, V3, V4, V5, V6/EDV, V7, V8/EDV and at V FU

End point values	experimental	Safety Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	102	102		
Units: N/A	103	102		

Statistical analyses

No statistical analyses for this end point

Secondary: vital sign

End point title	vital sign

End point description:

- Systolic blood pressure 1st, 2nd and 3rd measurements (mmHg)
- Diastolic blood pressure 1st, 2nd and 3rd measurements (mmHg)

- Pulse rate 1st, 2nd and 3rd measurements (bpm)
- Weight (kg)
- Height (cm)

End point type	Secondary

End point timeframe:

Collected at V1a, V2, V3, V4, V5, V6/EDV, V7 and at V8/EDV

End point values	experimental	Safety Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	103	102		
Units: mmHg, mmHg, bpm, kg, cm	102	102		

Statistical analyses

No statistical analyses for this end point

Secondary: Gynaecological Examination and Intravaginal Ultrasound

End point title	Gynaecological Examination and Intravaginal Ultrasound

End point description:

The gynaecological examination comprises inspection of:
- Internal genitals
- External genitals
- Breasts.

Intravaginal ultrasound comprises inspection of:
- Uterus
- Endometrium
- Ovaries.

End point type	Secondary

End point timeframe:

Gynaecological examination, including intravaginal ultrasound assessments at Visit 1a, Visit 6/EDV and at Visit 8/EDV and will be summarised at Visit 1a,Visit 6/EDV, Visit 8/EDV and at endpoint

End point values	experimental	Safety Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	103	102		
Units: N/A	102	102		

Statistical analyses

No statistical analyses for this end point

Secondary: physical examination findings

End point title	physical examination findings

End point description:

Comprises inspection of:
- General appearance
- Eyes, ears, nose and throat
- Lung/chest
- Heart
- Abdomen
- Pelvic
- Back
- Thyroid
- Lymph nodes
- Skin
- Extremities (incl. lower legs)
- Other

End point type	Secondary

End point timeframe:

Visit 1a, Visit 6/EDV and at Visit 8/EDV

End point values	experimental	Safety Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	103	102		
Units: N/A	102	102		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal bleeding pattern over 13 cycles (subject diaries)

End point title	Vaginal bleeding pattern over 13 cycles (subject diaries)

End point description:

Analysis of the vaginal bleeding pattern over 13 cycles will be performed in the same manner as for the vaginal bleeding pattern over 6 cycles in the core phase

End point type	Secondary

End point timeframe:

over 13 cycles

End point values	experimental	Safety Set	Per Protocol Set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	103	102	87	
Units: number of subjects	103	102	87	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first administration of the IMP to 14 days after the last administration of the IMP (FPFV: 22-May-2014; LPLV: 19-Sep-2016)

Adverse event reporting additional description:

TEAEs leading to trial termination were obtained from the AE form where the field "Action taken on trial treatment" was indicated as "drug withdrawn"

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

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	2 / 102 (1.96%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint dislocation	Additional description: Trauma due to high jump with the left shoulder luxation		
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pharyngitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 102 (70.59%)		

Investigations Weight increased subjects affected / exposed occurrences (all)	 3 / 102 (2.94%) 3		
Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	 2 / 102 (1.96%) 2 2 / 102 (1.96%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 6 / 102 (5.88%) 11		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all)	 3 / 102 (2.94%) 4 2 / 102 (1.96%) 4		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 2 / 102 (1.96%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal distension	 6 / 102 (5.88%) 11 5 / 102 (4.90%) 6 3 / 102 (2.94%) 5		

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Tooth impacted subjects affected / exposed occurrences (all)	3 / 102 (2.94%) 4 3 / 102 (2.94%) 4 2 / 102 (1.96%) 3 2 / 102 (1.96%) 2		
Reproductive system and breast disorders Metrorrhagia subjects affected / exposed occurrences (all) Dysmenorrhoea subjects affected / exposed occurrences (all) Breast pain subjects affected / exposed occurrences (all)	 5 / 102 (4.90%) 5 4 / 102 (3.92%) 5 2 / 102 (1.96%) 3		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 3 / 102 (2.94%) 3		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 7 / 102 (6.86%) 7 2 / 102 (1.96%) 2		
Psychiatric disorders Mood altered subjects affected / exposed occurrences (all)	 3 / 102 (2.94%) 4		

Anxiety			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	3		
Mood swings			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 102 (12.75%)		
occurrences (all)	18		
Respiratory tract infection viral			
subjects affected / exposed	7 / 102 (6.86%)		
occurrences (all)	7		
Bronchitis			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Viral infection			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	3		
Gastroenteritis			

subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2014	Global Protocol Amendment No.1, Final Version 1.0, 06-JUN-2014 was prepared based on the Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan for LF111 (drospirenone). The following changes were implemented: The coordinating investigator from the Netherlands was replaced by one from Finland. Final Version no. 1.0, 10-MAR-2017 CONFIDENTIAL Page 53 of 125 The Dutch CCMO did not approve the trial, thus Sweden was added. Inclusion criterion no 8 "Subjects willing to use an oral contraceptive for at least six cycles" was discarded, to emphasize the voluntary nature of trial participation. At V6, an eligibility check for the extension phase was added. V7 (at the start of cycle 10) was changed from a telephone visit to an on-site visit. Two additional telephone visits V6a (mid of cycle 8) and V7a (end of cycle 11) were added. Handling of the home pregnancy tests at V6a and V7a was added. Documentation of the IMP intake and vaginal bleeding pattern in the diary during the extension phase (cycles 7-13) was added. The possibility to also send a text message to the site on the day of the first IMP intake was added. Eight questions regarding IMP acceptability at V6/EDV and V8/EDV were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: