Clinical trial results:
Multicentre, phase II, open label randomised clinical trial to assess the bleeding profile, tolerability and safety associated with the use of three prolonged release formulations containing a combination of dienogest and ethinyl estradiol versus a flexible regimen contraceptive containing drospirenone 3 mg and ethinyl estradiol 20 µg.

Summary

EudraCT number	2016-003831-39
Trial protocol	LT CZ
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	22 October 2020
First version publication date	22 October 2020

Trial information

Trial identification

Sponsor protocol code	LPRI421-202

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Exeltis France
Sponsor organisation address	7 rue Victor Hugo, Sevres/Paris, France, 92310
Public contact	Project leader, Exeltis France S.A., 0033 14 9662 219 , ecoli@exeltis.com
Scientific contact	Project leader, Exeltis France S.A., 0033 14 9662 219 , ecoli@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	24 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess vaginal bleeding pattern (subject paper diaries).

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

The purpose of the trial was to demonstrate improved safety and tolerability of LPRI421 due to its prolonged release formulation and the lower hormone doses and to establish the most appropriate doses. Velmari® Langzyklus as an authorised COC for extended-regimen was chosen as an active comparator to demonstrate that LPRI421 is at least as safe as commonly used hormonal contraceptives and that the prolonged release formulation may even improve safety and tolerability.

Actual start date of recruitment	01 April 2017
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	Czech Republic: 119
Country: Number of subjects enrolled	Lithuania: 88
Country: Number of subjects enrolled	Ukraine: 138
Worldwide total number of subjects	345
EEA total number of subjects	207

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)	345
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female healthy subjects aged 18 to 35 years with regular menstrual cycles during the last three months or at least three complete menstrual cycles after delivery/abortion/miscarriage, if pregnant within the last six months prior to entering this trial and willing to use an oral contraceptive for two extended 91-day treatment periods.

Pre-assignment

Screening details:

Female subjects 18-35 y., regular cycles during the last three months before consent, when not using hormonal contraception, at least 3 complete menstrual cycles after delivery/abortion/miscarriage (only women who were pregnant within the last 6 months), BMI: 18 kg/m2 ≤ BMI < 30 kg/m2, Systolic blood pressure < 140 mmHg and diastolic BP < 90 mmHg..

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IMP 1

Arm description:

Subjects recieving IMP 1

Arm type	Experimental
Investigational medicinal product name	Dienogest (DNG)/ethinyl estradiol (EE) 1 mg/10 ug tablets
Investigational medicinal product code	LPRI421 D1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration once daily at approximately the same time each day. The duration of treatment for the individual subject was of 182 days.

Arm title	IMP 2

Arm description:

Subjects recieving IMP 2

Arm type	Experimental
Investigational medicinal product name	Dienogest (DNG)/ethinyl estradiol (EE) 2 mg/10 ug tablets
Investigational medicinal product code	LPRI421 D2
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration once daily at approximately the same time each day. The duration of treatment for the individual subject was of 182 days.

Arm title	IMP 3

Arm description:

subjects recieving IMP 3

Arm type	Experimental

Investigational medicinal product name	Dienogest (DNG)/ethinyl estradiol (EE) 2 mg/20 ug tablets
Investigational medicinal product code	LPRI421 D3
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration once daily at approximately the same time each day. The duration of treatment for the individual subject was of 182 days.

Arm title	Reference

Arm description:

Subjects taking reference product

Arm type	Active comparator
Investigational medicinal product name	Velmari Langzyklus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Blister with 24 Velmari® Langzyklus tablets containing drospirenone (DRSP)/EE 3 mg/20 µg ("Velmari"). Oral administration once daily at approximately the same time each day. The duration of treatment for the individual subject was of 182 days.

Number of subjects in period 1	IMP 1	IMP 2	IMP 3
Started	86	84	87
Completed	70	77	75
Not completed	16	7	12
Consent withdrawn by subject	-	3	3
Adverse event, non-fatal	11	3	7
Pregnancy or wish for pregnancy	1	1	-
Lost to follow-up	4	-	1
Ineligibiltiy/develpment of an exclusion criteria	-	-	1
not specified	-	-	-

Number of subjects in period 1	Reference
Started	88
Completed	77
Not completed	11
Consent withdrawn by subject	4
Adverse event, non-fatal	5
Pregnancy or wish for pregnancy	-
Lost to follow-up	-
Ineligibiltiy/develpment of an exclusion criteria	-
not specified	2

Baseline characteristics

Reporting groups	
Reporting group title	IMP 1
Reporting group description: Subjects recieving IMP 1	
Reporting group title	IMP 2
Reporting group description: Subjects recieving IMP 2	
Reporting group title	IMP 3
Reporting group description: subjects recieving IMP 3	
Reporting group title	Reference
Reporting group description: Subjects taking reference product	

Reporting group values	IMP 1	IMP 2	IMP 3
Number of subjects	86	84	87
Age categorical Units: Subjects			
Adults (18-35)	86	84	87
Gender categorical Units: Subjects			
Female	86	84	87

Reporting group values	Reference	Total	
Number of subjects	88	345	
Age categorical Units: Subjects			
Adults (18-35)	88	345	
Gender categorical Units: Subjects			
Female	88	345	

Subject analysis sets	
Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: all subjects who signed informed consent	
Subject analysis set title	Randomised Set
Subject analysis set type	Per protocol
Subject analysis set description: all subjects who were randomised	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: all subjects who were randomised and received at least one dose of IMP Additionally, subjects who were	

randomised, but IMP intake was not documented in any source and unused blisters were not returned, were included in safety set as well

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

Subject analysis set description:

all subjects who were included in the SS and completed the trial as intended without any major protocol deviation

Reporting group values	Enrolled Set	Randomised Set	Safety Set
Number of subjects	345	345	338
Age categorical Units: Subjects			
Adults (18-35)	400	345	338
Gender categorical Units: Subjects			
Female	400	345	338

Reporting group values	Per Protocol Set		
Number of subjects	266		
Age categorical Units: Subjects			
Adults (18-35)	266		
Gender categorical Units: Subjects			
Female	266		

End points

End points reporting groups

Reporting group title	IMP 1
Reporting group description: Subjects recieving IMP 1	
Reporting group title	IMP 2
Reporting group description: Subjects recieving IMP 2	
Reporting group title	IMP 3
Reporting group description: subjects recieving IMP 3	
Reporting group title	Reference
Reporting group description: Subjects taking reference product	
Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: all subjects who signed informed consent	
Subject analysis set title	Randomised Set
Subject analysis set type	Per protocol
Subject analysis set description: all subjects who were randomised	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: all subjects who were randomised and received at least one dose of IMP Additionally, subjects who were randomised, but IMP intake was not documented in any source and unused blisters were not returned, were included in safety set as well	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: all subjects who were included in the SS and completed the trial as intended without any major protocol deviation	

Primary: Total number of bleeding/spotting days

End point title	Total number of bleeding/spotting days[1]
End point description: The primary endpoint of this trial was the total number of bleeding/spotting days during the trial (overall and by extended treatment period).	
End point type	Primary
End point timeframe: For 91-day treatment period: - 0-5 days - 6-10 days - 11-15 days - >15 days For the complete trial treatment phase overall: - 0-10 days - 11-20 days - 21-30 days - >30 days	

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: No hypothesis testing was performed in this trial

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	68	68	88
Units: days	58	68	68	88

End point values	Per Protocol Set			
Subject group type	Subject analysis set			
Number of subjects analysed	266			
Units: days	266			

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of scheduled bleeding/spotting days

End point title	Total number of scheduled bleeding/spotting days

End point description:

End point type	Secondary

End point timeframe:

It was measured at the end of first period of 91 days and at the end of the trial at day 182

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	82	86	86
Units: days	84	82	86	86

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	338			
Units: days	338			

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of bleeding/spotting episodes

End point title	Total number of bleeding/spotting episodes

End point description:

End point type	Secondary

End point timeframe:

It was measured at the end of first period of 91 days and at the end of the trial at day 182

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	82	86	86
Units: episodes	84	82	86	86

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	338			
Units: episodes	338			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of bleeding/spotting episodes

End point title	Duration of bleeding/spotting episodes

End point description:

End point type	Secondary

End point timeframe:

It was measured at the end of first period of 91 days and at the end of the trial at day 182

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	82	86	86
Units: days	84	82	86	86

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	338			
Units: days	338			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of bleeding/spotting episodes

End point title	Intensity of bleeding/spotting episodes

End point description:

End point type	Secondary

End point timeframe:

It was measured at the end of first period of 91 days and at the end of the trial at day 182

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	82	86	86
Units: episodes with intensity	84	82	86	86

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	338			
Units: episodes with intensity	338			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of absence of all bleeding/spotting

End point title	Rate of absence of all bleeding/spotting

End point description:

End point type	Secondary

End point timeframe:

It was measured at the end of first period of 91 days and at the end of the trial at day 182

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	82	86	86
Units: percentage	84	82	86	86

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	338			
Units: percentage	338			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent adverse events (TEAEs)

End point title	Treatment-emergent adverse events (TEAEs)

End point description:

Only TEAEs, defined as AEs with onset or worsening after first intake of IMP until 14 days after last intake of IMP, were taken into account for the safety analysis

End point type	Secondary

End point timeframe:

During the trial

End point values	IMP 1	IMP 2	IMP 3	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	82	86	86
Units: events	84	82	86	86

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	338			
Units: events	338			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: during the trial	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Treatment IMP1
Reporting group description: -	
Reporting group title	Treatment IMP2
Reporting group description: -	
Reporting group title	Treatment IMP 3
Reporting group description: -	
Reporting group title	Treatment Reference Product
Reporting group description: -	

Serious adverse events	Treatment IMP1	Treatment IMP2	Treatment IMP 3
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 84 (3.57%)	0 / 82 (0.00%)	1 / 86 (1.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	1 / 86 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis superficial			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pyelonephritis acute			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment Reference Product		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 86 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombophlebitis superficial			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Pyelonephritis acute			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment IMP1	Treatment IMP2	Treatment IMP 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 84 (26.19%)	20 / 82 (24.39%)	15 / 86 (17.44%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 84 (0.00%)	2 / 82 (2.44%)	6 / 86 (6.98%)
occurrences (all)	0	2	7
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	8 / 84 (9.52%)	7 / 82 (8.54%)	5 / 86 (5.81%)
occurrences (all)	9	9	5
Breast pain			

subjects affected / exposed	4 / 84 (4.76%)	3 / 82 (3.66%)	2 / 86 (2.33%)
occurrences (all)	4	3	2
Cervical dysplasia			
subjects affected / exposed	4 / 84 (4.76%)	2 / 82 (2.44%)	2 / 86 (2.33%)
occurrences (all)	4	2	2
Vaginal infection			
subjects affected / exposed	1 / 84 (1.19%)	2 / 82 (2.44%)	3 / 86 (3.49%)
occurrences (all)	1	2	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 84 (1.19%)	0 / 82 (0.00%)	3 / 86 (3.49%)
occurrences (all)	1	0	3
Respiratory, thoracic and mediastinal disorders			
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 84 (3.57%)	2 / 82 (2.44%)	2 / 86 (2.33%)
occurrences (all)	3	2	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 84 (3.57%)	1 / 82 (1.22%)	2 / 86 (2.33%)
occurrences (all)	3	1	3
Tonsillitis			
subjects affected / exposed	4 / 84 (4.76%)	1 / 82 (1.22%)	0 / 86 (0.00%)
occurrences (all)	4	1	0
Sinusitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 82 (0.00%)	1 / 86 (1.16%)
occurrences (all)	0	0	1
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	5 / 84 (5.95%)	3 / 82 (3.66%)	5 / 86 (5.81%)
occurrences (all)	6	3	5

Non-serious adverse events	Treatment Reference Product		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 86 (25.58%)		
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	10		
Breast pain			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Cervical dysplasia			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Vaginal infection			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences (all)	4		
Tonsillitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	3 / 86 (3.49%)		
occurrences (all)	3		
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		

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