Clinical trial results:
Single center, phase II, open label randomized clinical trial to evaluate the inhibition of ovulation of three prolonged release formulations containing a combination of Dienogest and Ethinyl Estradiol versus a flexible regimen contraceptive containing drospirenone 3mg and Ethinyl Estradiol 20µg in 100 healthy women.

Summary

EudraCT number	2016-003830-26
Trial protocol	DE
Global end of trial date	06 February 2018

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	LPRI-421/201

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, France, 92310
Public contact	Project leader, Chemo Research, +34 917711500, covadonga.paneda@exeltis.com
Scientific contact	Project leader, Chemo Research, +34 917711500, covadonga.paneda@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	06 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the inhibition of ovarian activity (Hoogland Score) of LPRI-421 compared with Velmari® Langzyklus in Treatment Cycle 1 and Treatment Cycle 4.

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator: -

Actual start date of recruitment	02 March 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	Germany: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 02 March 2017 and 06 February 2018. A total of 150 subjects were enrolled in the study and screened. One hundred subjects were randomized and received at least 1 dose of IMP, and 84 subjects completed the study. Sixteen subjects discontinued their study participation

Pre-assignment

Screening details:

Fifty subjects were screening failures: 41 subjects did not meet the inclusion/exclusion criteria 4 were not randomized because the maximum number of subjects in the preferred group had been reached, and 3 withdrew their consent in the screening phase. Two subjects were lost to follow-up in the screening phase

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment 1 (T1)

Arm description:

EE/DNG 10 ug/1 mg

Arm type	Experimental
Investigational medicinal product name	EE/DNG 10 ug/1 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contains 10 ug of Ethinyl estradiol and 1 mg of Dienogest.
Subjects were asked to take their daily IMP for a period of 87 consecutive days followed by a 4-day pill-free period and then a further 28 consecutive days of active treatment.
The first dose was taken on the first or second day of the next menses following the pretreatment cycle, depending on the time of day the menses started. Subjects had to have a negative home pregnancy test before intake of the first dose on the first dosing day. Tablets were taken with a drink, with or without food.
Missed tablets were taken as soon as the subject remembered, even if this resulted in 2 tablets being taken on the same day. If vomiting or diarrhea occurred in first 4 hours after taking the tablet, subjects had to take a reserve tablet as soon as the vomiting/diarrhea had stopped.

Arm title	Treatment 2 (T2)

Arm description:

EE/DNG 10 ug/2 mg

Arm type	Experimental
Investigational medicinal product name	EE/DNG 10 ug/2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contains 10 ug of Ethinyl estradiol and 2 mg of Dienogest.
Subjects were asked to take their daily IMP for a period of 87 consecutive days followed by a 4-day pill-free period and then a further 28 consecutive days of active treatment.

The first dose was taken on the first or second day of the next menses following the pretreatment cycle, depending on the time of day the menses started. Subjects had to have a negative home pregnancy test before intake of the first dose on the first dosing day. Tablets were taken with a drink, with or without food.
Missed tablets were taken as soon as the subject remembered, even if this resulted in 2 tablets being taken on the same day. If vomiting or diarrhea occurred in first 4 hours after taking the tablet, subjects had to take a reserve tablet as soon as the vomiting/diarrhea had stopped.

Arm title	Treatment 3 (T3)

Arm description:

EE/DNG 20 ug/2 mg

Arm type	Experimental
Investigational medicinal product name	EE/DNG 20 ug/2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contains 20 ug of Ethinyl estradiol and 2 mg of Dienogest.
Subjects were asked to take their daily IMP for a period of 87 consecutive days followed by a 4-day pill-free period and then a further 28 consecutive days of active treatment.
The first dose was taken on the first or second day of the next menses following the pretreatment cycle, depending on the time of day the menses started. Subjects had to have a negative home pregnancy test before intake of the first dose on the first dosing day. Tablets were taken with a drink, with or without food.
Missed tablets were taken as soon as the subject remembered, even if this resulted in 2 tablets being taken on the same day. If vomiting or diarrhea occurred in first 4 hours after taking the tablet, subjects had to take a reserve tablet as soon as the vomiting/diarrhea had stopped.

Arm title	Velmari

Arm description:

Velmari Langzyklus

Arm type	Active comparator
Investigational medicinal product name	Velmari® Langzyklus 0.02/3 mg tablets (EE 20 µg/drospirenone 3 mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contains Ethinylestradiol 20 µg and drospirenone 3 mg.
Subjects were asked to take their daily IMP for a period of 87 consecutive days followed by a 4-day pill-free period and then a further 28 consecutive days of active treatment.
The first dose was taken on the first or second day of the next menses following the pretreatment cycle, depending on the time of day the menses started. Subjects had to have a negative home pregnancy test before intake of the first dose on the first dosing day. Tablets were taken with a drink, with or without food.
Missed tablets were taken as soon as the subject remembered, even if this resulted in 2 tablets being taken on the same day. If vomiting or diarrhea occurred in first 4 hours after taking the tablet, subjects had to take a reserve tablet as soon as the vomiting/diarrhea had stopped.

Number of subjects in period 1	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)
Started	25	25	25
Completed	22	22	22
Not completed	3	3	3
Intake of prohibited medication	-	-	1
Physician decision	-	-	-
Adverse event, non-fatal	2	2	-
Use of emerg. contracep in posttreatment cycles	-	-	1
Unavailability for visit schedule	1	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	Velmari
Started	25
Completed	18
Not completed	7
Intake of prohibited medication	-
Physician decision	1
Adverse event, non-fatal	3
Use of emerg. contracep in posttreatment cycles	-
Unavailability for visit schedule	2
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	100	100	
Age categorical Units: Subjects			
Adults (18 - 35)	100	100	
Gender categorical Units: Subjects			
Female	100	100	

Subject analysis sets

Subject analysis set title	Safety analysis (SA) set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis (SA) set included all subjects who were randomized and received at least 1 dose of the study product. Treatment assignment was based on the treatment actually received.

Subject analysis set title	Full Analysis (FA) set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis (FA) set included all subjects of the SA set with at least 1 measurement of the primary efficacy variable

Subject analysis set title	Per Protocol (PP) analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) set included all subjects of the FA set for whom no major protocol deviations were documented

Reporting group values	Safety analysis (SA) set	Full Analysis (FA) set	Per Protocol (PP) analysis Set
Number of subjects	100	98	86
Age categorical Units: Subjects			
Adults (18 - 35)	100	98	86
Gender categorical Units: Subjects			
Female	100	98	86

End points

End points reporting groups

Reporting group title	Treatment 1 (T1)
Reporting group description: EE/DNG 10 ug/1 mg	
Reporting group title	Treatment 2 (T2)
Reporting group description: EE/DNG 10 ug/2 mg	
Reporting group title	Treatment 3 (T3)
Reporting group description: EE/DNG 20 ug/2 mg	
Reporting group title	Velmari
Reporting group description: Velmari Langzyklus	
Subject analysis set title	Safety analysis (SA) set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis (SA) set included all subjects who were randomized and received at least 1 dose of the study product. Treatment assignment was based on the treatment actually received.	
Subject analysis set title	Full Analysis (FA) set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis (FA) set included all subjects of the SA set with at least 1 measurement of the primary efficacy variable	
Subject analysis set title	Per Protocol (PP) analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol (PP) set included all subjects of the FA set for whom no major protocol deviations were documented	

Primary: Hoogland score

End point title	Hoogland score[1]
End point description: It reflects the ovarian status and will be assessed per cycle based on data from multiple serum analyses of estradiol and progesterone and by multiple ovarian follicle size measurements by TVU at the scheduled visits during the 1st and 4th treatment cycle. The Hoogland score combines follicle size in mm and progesterone/estradiol serum concentrations in nmol/L The maximum Hoogland score observed during the study was used for the efficacy assessment. Three categories were defined based on the Hoogland score: Categories 1 and 2 (scores 1 to 4) were classified as “inhibition of ovulation” for the efficacy assessment.	
End point type	Primary
End point timeframe: Treatment Cycle (TC) 1 and Treatment Cycle (TC) 4	

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: All efficacy parameters were analyzed descriptively per treatment group. No statistical tests were planned

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[2]	24[3]	25[4]	24[5]
Units: mm; nmol/L				
scores 1 to 4: inhibition of ovulation	24	24	25	24
scores 5 to 6: no inhibition of ovulation	1	0	0	0

Notes:

[2] - results for TC 4: inh of ovulation 20 and no inh of ovulation 2

[3] - For TC 4: inh of ovulation 21 and no inh of ovulation 1

[4] - For TC 4: inhibition of ovulation 22 and no inhibition of ovulation 0

[5] - For TC 4: Inhibition of ovulation 20 and No inh of ovulation 0

End point values	Full Analysis (FA) set	Per Protocol (PP) analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	86		
Units: mm; nmol/L				
scores 1 to 4: inhibition of ovulation	83	83		
scores 5 to 6: no inhibition of ovulation	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Landgren Score

End point title	Landgren Score

End point description:

The Landgren score is based on the serum progesterone measurements at the scheduled visits. The Landgren score was determined in TC 1 and TC 4 if an ovulation was suspected in the TVU examination and if the corresponding Hoogland score was 5 or 6, and additionally in a T1 subject with a Hoogland score of 4 in TC 4 based on the investigator's decision. Thus, there were 5 Landgren score determinations in total (T1: 4 cases; T2: 1 case). The Landgren score was positive in one T1 subject during TC 4 and negative in all other cases.

End point type	Secondary

End point timeframe:

TC1 and TC4

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[6]	24[7]	25[8]	24[9]
Units: positive/negative				
Positive	0	0	0	0
Negative	1	0	0	0
Not analyzed	24	24	25	24

Notes:

[6] - in TC 4: 1 Positive; 2 Negative; 19 Not analyzed

[7] - In TC 4: 0 positive; 1 negative; 22 not analyzed

[8] - In TC 4: 0 positive; 0 negative; 23 not analyzed

[9] - In TC 4: 0 positive; 0 negative; 22 not analyzed

End point values	Full Analysis (FA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	98[10]			
Units: positive/negative				
Positive	0			
Negative	1			
Not analyzed	97			

Notes:

[10] - In TC 4: 1 positive; 3 negative; 86 not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Insler Score

End point title	Insler Score

End point description:

The cervix condition will be evaluated by means of the Insler Score during the precycle, TC 1 and TC 4 whenever a follicle size ≥13 mm. The Insler Score was developed and used as an instrument for timing fertilization and reflects the cervical condition for a possible ascension of the sperms. High values correspond to an excellent condition for sperm ascension under high estrogen influence during ovulation and low values mean worse condition for sperm ascension.
The Insler Score comprises the following criteria: a) cervix status by inspection; b) amount of mucus by inspection; c) spinnability of the mucus by spreading a mucus sample in a sponge forceps; d) ferning by microscopy.
The following evaluation will be made based on the Insler scoring criteria:
0 - 3 points = negative
4 - 6 points = slight
7 - 9 points = moderate
10 - 12 points = full

End point type	Secondary

End point timeframe:

TC1 and TC4

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[11]	24[12]	25[13]	24[14]
Units: points				
full	1	0	0	0
moderate	3	3	0	2
negative/slight	21	21	25	22

Notes:

[11] - for TC 4: 1 Full; 7 Moderate; 17 negative/slight

[12] - for TC 4: 0 Full; 1 Moderate; 23 negative/slight

[13] - for TC 4: 0 Full; 1 Moderate; 24 negative/slight

[14] - for TC 4: 0 Full; 1 Moderate; 23 negative/slight

End point values	Full Analysis (FA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	98[15]			
Units: points				
full	1			
moderate	8			
negative/slight	89			

Notes:

[15] - for TC 4: 1 Full; 10 Moderate; 87 negative/slight

Statistical analyses

No statistical analyses for this end point

Secondary: Transvaginal ultrasound

End point title	Transvaginal ultrasound

End point description:

The TVU will assess the reproductive organs including the uterus, cervix, endometrium and follicle diameter (left and right ovary). Any abnormalities detected in the bladder will be documented however inspection of the bladder is not routine at every visit. The Douglas pouch will be assessed during screening and at the final examination.
The maximum follicle diameter and endometrial thickness will be recorded for both ovaries in the eCRF. Any abnormalities seen must be documented.

End point type	Secondary

End point timeframe:

Uterus condition: at screening and final examination
Endometrial Thickness: at each visit
Mean diameter of largest follicle: D12 of pretreatment and D27 of posttreatment

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	24	25	24
Units: N/A	25	24	25	24

End point values	Full Analysis (FA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: N/A	98			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum levels of progesterone (P4), E2, FSH and LH

End point title	Serum levels of progesterone (P4), E2, FSH and LH

End point description:

Serum levels of progesterone were used for (a) determining the Hoogland score; (b) confirming a sonographically suspected ovulation; and (c) determining the Landgren score.

End point type	Secondary

End point timeframe:

Progesterone: T1 (TC3), T2 (TC4), T3 (TC1), Velmari: (TC4)
Estradiol: T1 (TC4), T2 (TC4), T3 (TC4), Velmari: (TC1)
FSH: T1 (TC1), T2 (TC1), T3 (TC4), Velmari: (TC1)
LH: T1 (TC4), T2 (TC4), T3 (TC4), Velmari: (TC1)

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	24	25	24
Units: nmol/L	25	24	25	24

End point values	Full Analysis (FA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: nmol/L	98			

Statistical analyses

No statistical analyses for this end point

Secondary: vital signs

End point title	vital signs

End point description:

End point type	Secondary

End point timeframe:

Vital signs (including heart rate, systolic and diastolic blood pressure) will be summarized using

descriptive statistics at run in/screening phase and at each post-screening time point.

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	25	25
Units: N/A	25	25	25	25

End point values	Safety analysis (SA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: N/A	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Laboratory Evaluation

End point title	Clinical Laboratory Evaluation

End point description:

End point type	Secondary

End point timeframe:

Laboratory parameters (clinical chemistry, haematology, serology (HBsAg, HBV, HCV and HIV) and urinalysis) will be summarized using descriptive statistics at run in/screening phase and at each post-screening time point.

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	25	25
Units: N/A	25	25	25	25

End point values	Safety analysis (SA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: N/A	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

All adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. If it cannot be determined whether the AE is treatment emergent due to a partial onset date then it will be counted as such

End point type	Secondary

End point timeframe:

AEs should be reported up to 28 days after the last adm of the IMP. Also, any reportable AEs that are unresolved at the subject's LV in the study will be FU by the Investigator for as long as medically indicated, but without further recording in the eCRF

End point values	Treatment 1 (T1)	Treatment 2 (T2)	Treatment 3 (T3)	Velmari
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	25	25
Units: N/A	25	25	25	25

End point values	Safety analysis (SA) set			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: N/A	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs should be reported up to 28 days after the last administration of the IMP. Also, Any reportable AEs that are unresolved at the subject's last visit in the study will be followed up by the Investigator for as long as medically indicated.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

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	1 / 100 (1.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 100 (99.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			

subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	5		
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Endodontic procedure			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Jaw operation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 100 (10.00%)		
occurrences (all)	11		
Peripheral swelling			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Chest discomfort			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Sensitivity to weather change			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Swelling			

subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Vessel puncture site haematoma			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	17 / 100 (17.00%)		
occurrences (all)	17		
Ovarian cyst			
subjects affected / exposed	13 / 100 (13.00%)		
occurrences (all)	20		
Breast enlargement			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	6		
Dysmenorrhoea			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	9		
Vulvovaginal pruritus			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	4		
Vaginal haemorrhage			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Breast pain			

subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Pelvic pain			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Vaginal discharge			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	3		
Vulvovaginal dryness			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Breast tenderness			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Endometrial hyperplasia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Fibrocystic breast disease			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Menorrhagia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Vulvovaginal discomfort			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Vulvovaginal pain			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Oropharyngeal pain			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Dry throat			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Psychiatric disorders			
Mood altered			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	7		
Affective disorder			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	4		
Irritability			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	6		
Libido decreased			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Anxiety			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	4		
Alanine aminotransferase increased			

subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Blood urea decreased			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Nitrite urine present			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	3		
Blood bilirubin increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Platelet count increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Protein total decreased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	5		
Contusion			

subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Sunburn			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Arthropod sting			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Traumatic haematoma			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	49 / 100 (49.00%)		
occurrences (all)	124		
Dizziness			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	20 / 100 (20.00%)		
occurrences (all)	30		
Nausea			
subjects affected / exposed	14 / 100 (14.00%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	13 / 100 (13.00%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	11 / 100 (11.00%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	4		
Flatulence			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Toothache			

subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Douglas' pouch mass			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Swollen tongue			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	11 / 100 (11.00%)		
occurrences (all)	12		
Alopecia			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	4		
Blister			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		

Seborrhoea			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Skin odour abnormal			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	13 / 100 (13.00%)		
occurrences (all)	14		
Leukocyturia			
subjects affected / exposed	12 / 100 (12.00%)		
occurrences (all)	14		
Dysuria			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Ketonuria			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Proteinuria			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Micturition urgency			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	5		
Arthralgia			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Neck pain			

subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	62 / 100 (62.00%)		
occurrences (all)	76		
Vulvovaginal candidiasis			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Gastrointestinal infection			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	4		
Oral herpes			
subjects affected / exposed	4 / 100 (4.00%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	3		
Vaginal infection			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	4		
Candida infection			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	4		

Conjunctivitis subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Cystitis subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Eye abscess subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Infected bite subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Otitis externa subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 2		
Paronychia subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 100 (3.00%) 4		
Increased appetite subjects affected / exposed occurrences (all)	3 / 100 (3.00%) 3		
Fluid retention subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	- First visit subject is changed from January 2017 to 02-March-2017 - For PK compliance check blood samples will be taken at every visit during TC1 and TC4 and when the sonographically suspected ovulation is confirmed the EE concentration will be measured in 3 blood samples: day of sonographically suspected ovulation under treatment and in blood samples taken at the 2 previous visits (-3 days and -6 days). - blood volumes in laboratory analysis corrected. - other minor corrections to the protocol requested by the EC or for clarification

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported