Clinical trial results:
A prospective, randomized, parallel-group study to assess the effects on ovarian activity of ellaOne (ulipristal acetate 30 mg single dose) taken after three consecutive days of missed combined oral contraceptive pills

Summary

EudraCT number	2017-002283-41
Trial protocol	DE
Global end of trial date	28 May 2018

Results information

Result version number	v1 (current)
This version publication date	19 May 2019
First version publication date	19 May 2019

Trial information

Trial identification

Sponsor protocol code	151032-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratoire HRA Pharma
Sponsor organisation address	200 avenue de Paris, Chatillon, France, 92320
Public contact	Marlène Perret, Laboratoire HRA Pharma, 0033 184139257, m.perret@hra-pharma.com
Scientific contact	Marlène Perret, Laboratoire HRA Pharma, 0033 184139257, m.perret@hra-pharma.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	25 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2018
Global end of trial reached?	Yes
Global end of trial date	28 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the pharmacodynamic (PD) effects, and specifically on occurrence and timing of ovulation with pregnancy risk, of ellaOne taken after pills of combined oral contraception (COC) were missed for three consecutive days during the first week of COC use and were resumed either on the day of ellaOne intake or five days later.

Protection of trial subjects:

Subjects had to be withdrawn from study medication under the following circumstances:
• Pregnancy (every attempt must be made to follow up subjects who become pregnant to determine the outcome of the pregnancy),
• Serious intercurrent problems requiring admission to the critical care unit or surgery,
• Subject unable to comply with study visits or requirements,
• Suspected unexpected serious adverse reaction to study medication,
• Subject withdraws informed consent,
• Liver enzymes levels above three times the upper limit of normal at D1 or D15 of the EXP period,
• Upon discretion of the investigator in the event of a protocol violation (inclusion/ exclusion criteria).

Background therapy:

no Background therapy

Evidence for comparator:

No comparator

Actual start date of recruitment	08 January 2018
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: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The screening period was performed within a maximum of 28 days before start of Baseline period.
The Baseline period was performed after all screening assessments are checked by the investigator.
The Baseline period was from D1 to D28.
The randomization was performed at D29 (= V2: D1: 1st day of the Experimental period)

Pre-assignment

Screening details:

The women screened had a BMI <30.0 kg/m2, relied on a COC as their primary method of contraception for at least 2 cycles before they enter the baseline (B) period and were willing to continue with a COC for at least 1 cycle after end of experimental (EXP) period, must not be at risk of pregnancy and were willing to use condoms during the study.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The study is single-blind but blinding will be kept only until End of Study visit for the study site personnel in charge of performing TransVaginal Ultrasound (TVU).

Arms

Arm title	Baseline
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Levora®
Investigational medicinal product code	Levora®
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Baseline period:
- 1 active pill of Levora® (30 µg ethinyl estradiol / 150 µg levonorgestrel) taken every day during 21 days from D1 to D21 evenings.
- 1 inactive pill of Levora® taken every day during 7 days from D22 to D28 evenings.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study is single-blind but blinding will be kept only until End of Study visit for the study site personnel in charge of performing TransVaginal Ultrasound (TVU).

Number of subjects in period 1	Baseline
Started	65
Completed	54
Not completed	11
Subject not randomized for unavailability for stud	1
Subject withdrawn when the study was suspended fol	10

Period 2

Period 2 title	Experimental period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Blinding implementation details:

The study is single-blind but blinding will be kept only until End of Study visit for the study site personnel in charge of performing TransVaginal Ultrasound (TVU).

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm1: COC resumed on the day of UPA intake

Arm description:

Immediate resumption of combined oral contraception (COC) after pills of COC were missed for 3 consecutive days

Arm type	Experimental
Investigational medicinal product name	ellaOne® 30 mg
Investigational medicinal product code	UPA 30 mg
Other name	ella® 30 mg, ulipristal acetate 30 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Arm1 / Arm 2:
- 1 pill of 30 mg UPA taken at D8 morning.

Investigational medicinal product name	Levora®
Investigational medicinal product code	Levora®
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Arm 1 / Experimental period:
- 1 active pill of Levora® (30 µg ethinyl estradiol / 150 µg levonorgestrel) taken every day during 4 days from D1 to D4 evenings (Theoretical time of ella intake + 12h (+/- 30 min)).
- 1 active pill of Levora taken 12 hours (+/- 30 min) after ellaOne theoretical time of intake (i.e. on D8 evening), and 1 pill taken every day during 13 days, from D9 evening until D21 evening.
- 1 inactive pill of Levora® taken every day during 7 days from D22 to D28 evenings.

Arm title	Arm 2: COC resumed 5 days after UPA intake

Arm description:

Resumption of combined oral contraception (COC) after pills of COC were missed for 8 consecutive days (3+5 days).

Arm type	Experimental
Investigational medicinal product name	ellaOne® 30 mg
Investigational medicinal product code	UPA 30 mg
Other name	ella® 30 mg, ulipristal acetate 30 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Arm 1 / Arm 2:
- 1 pill of 30 mg UPA taken at D8 morning in EXP period.

Investigational medicinal product name	Levora®
Investigational medicinal product code	Levora®
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Arm 2 / Experimental period:
- 1 active pill of Levora (30 µg ethinyl estradiol / 150 µg levonorgestrel) taken every day during 4 days from D1 to D4 evenings (Theoretical time of ella intake + 12h (+/- 30 min)).
- 1 active pill of Levora taken 5 days and 12hours (+/- 30 min) after ellaOne® theoretical time of intake (i.e. on D13 evening).
- 1 active pill of Levora taken every evening during 8 days, from D14 evening until D21 evening.
- 1 inactive pill of Levora® taken every day during 7 days from D22 to D28 evenings.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study is single-blind but blinding will be kept only until End of Study visit for the study site personnel in charge of performing TransVaginal Ultrasound (TVU).

Number of subjects in period 2	Arm1: COC resumed on the day of UPA intake	Arm 2: COC resumed 5 days after UPA intake
Started	27	27
Completed	26	23
Not completed	1	4
Adverse event, non-fatal	-	2
Protocol deviation	1	2

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	65	65	
Age categorical			
All women aged 18-30 years old were screened			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	65	65	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	25		
full range (min-max)	18 to 30	-	
Gender categorical			
Units: Subjects			
Female	65	65	
Male	0	0	
Race			
Units: Subjects			
white	63	63	
Black	0	0	
Asian	0	0	
Bi-racial (White/Black)	1	1	
Other	1	1	
Demographic and baseline characteristics - BMI			
Units: kg/m²			
median	22.5		
full range (min-max)	18.1 to 29.9	-	

Subject analysis sets

Subject analysis set title	Arm1: COC resumed on the day of UPA intake
Subject analysis set type	Full analysis

Subject analysis set description:

All women who completed the study in Arm 1

Subject analysis set title	Arm 2: COC resumed 5 days after UPA intake

Subject analysis set type	Full analysis

Subject analysis set description:

All women who completed the study in Arm 2

Reporting group values	Arm1: COC resumed on the day of UPA intake	Arm 2: COC resumed 5 days after UPA intake	
Number of subjects	26	23	
Age categorical			
All women aged 18-30 years old were screened			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	23	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	25	23	
full range (min-max)	18 to 30	18 to 30	
Gender categorical			
Units: Subjects			
Female	26	23	
Male	0	0	
Race			
Units: Subjects			
white	25	23	
Black	0	0	
Asian	0	0	
Bi-racial (White/Black)	0	0	
Other	1	0	
Demographic and baseline characteristics - BMI			
Units: kg/m²			
median	24.3	21.9	
full range (min-max)	19.6 to 28.8	19.1 to 27.3	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: -	
Reporting group title	Arm1: COC resumed on the day of UPA intake
Reporting group description:	
Immediate resumption of combined oral contraception (COC) after pills of COC were missed for 3 consecutive days	
Reporting group title	Arm 2: COC resumed 5 days after UPA intake
Reporting group description:	
Resumption of combined oral contraception (COC) after pills of COC were missed for 8 consecutive days (3+5 days).	
Subject analysis set title	Arm1: COC resumed on the day of UPA intake
Subject analysis set type	Full analysis
Subject analysis set description:	
All women who completed the study in Arm 1	
Subject analysis set title	Arm 2: COC resumed 5 days after UPA intake
Subject analysis set type	Full analysis
Subject analysis set description:	
All women who completed the study in Arm 2	

Primary: Proportion of women at risk of pregnancy (OSp) during the EXP period

End point title	Proportion of women at risk of pregnancy (OSp) during the EXP period
End point description:	
Analysis 1: Proportion of women randomized, treated with ellaOne® and having completed their experimental period in Full Analysis Set either in arm 1 or arm 2 and who were (at any time from D1 to D28 during the Experimental period) an Ovarian Status at risk of Pregnancy	
End point type	Primary
End point timeframe:	
At any time from D1 to D28 during the Experimental period	

End point values	Arm1: COC resumed on the day of UPA intake	Arm 2: COC resumed 5 days after UPA intake		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: Pourcentage of women	0	17		

Statistical analyses

Statistical analysis title	Proportion of women who were at risk of pregnancy
Statistical analysis description:	
Proportion was estimated with their exact (Clopper-Pearson) two-sided 95% confidence interval.	
Comparison groups	Arm1: COC resumed on the day of UPA intake v Arm 2: COC resumed 5 days after UPA intake

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.042
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Primary: The time to ovulation with risk of pregnancy (time to OSp)

End point title	The time to ovulation with risk of pregnancy (time to OSp)

End point description:

Analysis 2: Evolution over time of the estimated probability of being ovulation free (K-M curves) was presented using the of time to event of each women.

End point type	Primary

End point timeframe:

At any time from D1 to D28 during the Experimental period

End point values	Arm1: COC resumed on the day of UPA intake	Arm 2: COC resumed 5 days after UPA intake		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: Pourcentage of women	0	17		

Statistical analyses

Statistical analysis title	Time to ovulation of women with risk of pregnancy

Statistical analysis description:

Evolution over time of the estimated probability of being ovulation free was presented using the Kaplan Mieir approach survival curves (proportion of event free women at each day) in each arm and use of the non-parametric logrank test for comparing both groups in the FAS population.

Comparison groups	Arm1: COC resumed on the day of UPA intake v Arm 2: COC resumed 5 days after UPA intake
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided

Secondary: The proportion of women who ovulated within the five days following ellaOne intake and were at risk of pregnancy (OSp) during the EXP period

End point title	The proportion of women who ovulated within the five days following ellaOne intake and were at risk of pregnancy (OSp) during the EXP period

End point description:

Analysis 3: Proportion of women randomized, treated with ellaOne® and having completed their experimental period in Full Analysis Set either in arm 1 or arm 2 and who ovulated within the five days following ellaOne intake and were at risk of pregnancy (OSp) during the EXP period

End point type	Secondary

End point timeframe:

At any time from D1 to D28 during the Experimental period

End point values	Arm1: COC resumed on the day of UPA intake	Arm 2: COC resumed 5 days after UPA intake		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: Pourcentage of women	0	0		

Statistical analyses

Statistical analysis title	Proportion of women who ovulated in 5 days

Statistical analysis description:

Proportion was estimated with their exact (Clopper-Pearson) two-sided 95% confidence interval.

Comparison groups	Arm1: COC resumed on the day of UPA intake v Arm 2: COC resumed 5 days after UPA intake
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [1]
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - Arm 1: 0% 95%CI [0 – 13.22]
Arm 2: 0% 96% CI [0 – 14.8]

Secondary: Occurrence rate of ovulation (from D1 to D28) at risk of pregnancy (OSp) during BSL period

End point title	Occurrence rate of ovulation (from D1 to D28) at risk of pregnancy (OSp) during BSL period

End point description:

Analysis 4: Proportion of women randomized, having missed three consecutive pills of COC, having completed their baseline period in Full Analysis Set either in arm 1 or arm 2 and show the occurrence rate of ovulation (from D1 to D28) at risk of pregnancy (OSp) during BSL period

End point type	Secondary

End point timeframe:

At any time from D1 to D28 during the baseline period

End point values	Arm1: COC resumed on the day of UPA intake	Arm 2: COC resumed 5 days after UPA intake		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: Pourcentage	0	0		

Statistical analyses

Statistical analysis title	Occurrence rate of ovulation at OSp during BSL

Statistical analysis description:

Rate will be estimated with its exact (Clopper-Pearson) two-sided 95% confidence interval.

Comparison groups	Arm1: COC resumed on the day of UPA intake v Arm 2: COC resumed 5 days after UPA intake
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1 [2]
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Notes:

[2] - NA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signature of the informed consent (from screening visit) to the last visit (end of study visit V7) planned in the protocol.

Adverse event reporting additional description:

Adverse events observed by the investigator or reported by the subject will be collected

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Safety set - All subjects

Reporting group description:

All the subjects included in analysis from D1 Baseline to end of study visit (V7) with informed consent signed.

Reporting group title	Safety Set - Arm 1

Reporting group description:

All women included in arm 1 who completed the study (arm 1 of the Full Analysis Set) from D1 Baseline to end of study visit (V7) with informed consent signed.

Reporting group title	Safety Set - Arm 2

Reporting group description:

All women included in arm 2 who completed the study (arm 2 of the Full Analysis Set) from D1 Baseline to end of study visit (V7) with informed consent signed.

Serious adverse events	Safety set - All subjects	Safety Set - Arm 1	Safety Set - Arm 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	0 / 27 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Safety set - All subjects	Safety Set - Arm 1	Safety Set - Arm 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 65 (86.15%)	23 / 27 (85.19%)	25 / 27 (92.59%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	6 / 65 (9.23%)	3 / 27 (11.11%)	3 / 27 (11.11%)
occurrences (all)	6	3	3

Aspartate Aminotransferase Increased			
subjects affected / exposed	5 / 65 (7.69%)	3 / 27 (11.11%)	2 / 27 (7.41%)
occurrences (all)	6	3	3
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 65 (4.62%)	1 / 27 (3.70%)	2 / 27 (7.41%)
occurrences (all)	3	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 65 (35.38%)	10 / 27 (37.04%)	10 / 27 (37.04%)
occurrences (all)	30	13	13
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	5 / 65 (7.69%)	2 / 27 (7.41%)	3 / 27 (11.11%)
occurrences (all)	5	2	3
Abdominal Pain Lower			
subjects affected / exposed	5 / 65 (7.69%)	2 / 27 (7.41%)	2 / 27 (7.41%)
occurrences (all)	5	2	2
Nausea			
subjects affected / exposed	6 / 65 (9.23%)	4 / 27 (14.81%)	2 / 27 (7.41%)
occurrences (all)	9	6	3
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	6 / 65 (9.23%)	3 / 27 (11.11%)	3 / 27 (11.11%)
occurrences (all)	7	3	4
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	5 / 65 (7.69%)	1 / 27 (3.70%)	4 / 27 (14.81%)
occurrences (all)	5	1	4
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 65 (7.69%)	3 / 27 (11.11%)	2 / 27 (7.41%)
occurrences (all)	5	3	2
Musculoskeletal and connective tissue disorders			
Back Pain			

subjects affected / exposed	2 / 65 (3.08%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	26 / 65 (40.00%)	13 / 27 (48.15%)	10 / 27 (37.04%)
occurrences (all)	30	15	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2017	Protocol dated on 07 December 2017 included additional specific: - Monitoring of Liver function test : Laboratory safety parameters (ALAT, ASAT, GGT, ALP, total bilirubin) were measured in addition to the screening, the following visits, on Day 1 and Day 15 of the Experimental period and at End-of-Study visit. - Exclusion criteria related to liver function and global study termination rules: Subjects presenting with any of the following were not to be included in the study: Liver enzymes levels at the screening visit above three times the upper limit of normal or any other anomalies in safety labs recognized as clinically significant by the investigator. For more additional information, please see section Interruption below.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 November 2017	Following reports of liver injuries cases observed with chronic use of Esmya (UPA 5 mg indicated for pre-operative treatment as well as intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age), the BfArM addressed HRA Pharma on 8 Nov 2017 a request for hearing before ordering withdrawal, revocation or suspension of approval of the clinical trial. BfArM also asked to stop recruiting any patients until clarification was made to what extent do these events influence the benefit-risk (B/R) assessment of ellaOne use and what measure should be taken to ensure safety of the patient. No patient had yet entered the study at time of BfArM request. Concomitantly an Article 20 safety referral procedure (EMEA/H/A-20/1460/C/2041/0043) was triggered by the EU Commission to review B/R of Esmya taking into consideration reports of liver injuries. Since no signal of liver injury were detected during the clinical development of UPA 30 mg in the emergency contraception indication and in post-marketing surveillance, HRA Pharma considered that the events reported with Esmya were not relevant for the single 30 mg dose administration and did not impact the B/R assessment of the ongoing trial. HRA suggested the BfArM to reconsider the suspension of this clinical trial and proposed revisions to the protocol (see section substantial protocol amendments, protocol dated 07 Dec 2017). This was considered acceptable by the BfArM who issued an authorisation letter on 18 Dec 2017. At the end of Article 20 safety referral procedure for Esmya, the EMA confirmed that "No cases of serious liver injury have been reported with ellaOne and there are no such concerns with this medicine at this time".	20 December 2017

Notes:

Limitations and caveats

None reported