Clinical trial results:
A prospective, randomized, double-blind parallel-arm, placebo-controlled study to assess the effects on ovarian activity of a combined oral contraceptive pill when preceded by the intake of ellaOne® (ulipristal acetate 30 mg) or placebo

Summary

EudraCT number	2011-005573-23
Trial protocol	SE NL GB
Global end of trial date	31 August 2012

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	2914-015

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	15 rue Béranger, Paris, France, 75003
Public contact	Medical Affairs department, Laboratoire HRA Pharma, 0033 140331130, d.levy@hra-pharma.com
Scientific contact	Medical Affairs department, Laboratoire HRA Pharma, 0033 140331130, d.levy@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	11 February 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2012
Global end of trial reached?	Yes
Global end of trial date	31 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the effects of quick starting a Combined Oral Contraceptive Pill (COCP) on follicular growth and hormonal parameters after ellaOne® or placebo intake.

Protection of trial subjects:

This trial was conducted in accordance with the GCPs guidelines, ethical principles of the Declaration of Helsinki and local applicable regulatory requirement(s). Additionally, it was conducted by scientifically and medically qualified persons who respected the rights and welfare of the subjects and after the protocol was approved by Ethics Committee in each country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2012
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	Netherlands: 45
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	76

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 3 study sites in the UK, Sweden and the Netherlands. The recruitement period started on 26 March 2012 and ended on 27 July 2012

Pre-assignment

Screening details:

103 subjects were screened (26, 21, 56 in UK, Sweden and Netherlands respectively). 27 subjects dropped out before inclusion for the following reasons: non respect of inclusion/exclusion criteria; ovary or follicle not visible or TVU couldn't be performed; subject not available for further visits; subject lost to FU; ICF withdrawal.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Blinding implementation details:

Treatment were delivered to eligible subjects in the ascending order of boxes numbers. A randomization schedule linking treatment numbers to treatment codes (ellaOne or Placebo) was generated by independent statistician but was not provided to sites. The sites only received the sealed envelopes corresponding to each treatment number that was sent to them.

Arms

Are arms mutually exclusive?	Yes
Arm title	ellaOne

Arm description:

Intake of 1 pill of ellaOne on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 (combined oral contraceptive pill (COCP)) for 21 consecutive days, starting on the day after ellaOne intake

Arm type	Experimental
Investigational medicinal product name	ellaOne
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet containing 30 mg micronized UPA was administered on site to women with water

Investigational medicinal product name	Microgynon 30
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet containing 30 µg ethinyl estradiol / 150 µg levonorgestrel was taken daily for 21 consecutive days, at approximately the same time every day

Arm title	Placebo

Arm description:

Intake of 1 pill of Placebo on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 for 21 consecutive days, starting on the day after Placebo intake

Arm type	Placebo

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

Dosage and administration details:

1 tablet of Placebo was administered on site to women with water

Investigational medicinal product name	Microgynon 30
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet containing 30 µg ethinyl estradiol / 150 µg levonorgestrel was taken daily for 21 consecutive days, at approximately the same time every day

Number of subjects in period 1	ellaOne	Placebo
Started	39	37
Completed	39	37

Baseline characteristics

Reporting groups	
Reporting group title	ellaOne
Reporting group description:	
Intake of 1 pill of ellaOne on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 (combined oral contraceptive pill (COCP)) for 21 consecutive days, starting on the day after ellaOne intake	
Reporting group title	Placebo
Reporting group description:	
Intake of 1 pill of Placebo on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 for 21 consecutive days, starting on the day after Placebo intake	

Reporting group values	ellaOne	Placebo	Total
Number of subjects	39	37	76
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Adults (18-64 years)	39	37	76
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	23.5	24.1	
standard deviation	± 2.7	± 3.4	-
Gender categorical			
Units: Subjects			
Female	39	37	76
Male	0	0	0

End points

End points reporting groups

Reporting group title	ellaOne
Reporting group description:	
Intake of 1 pill of ellaOne on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 (combined oral contraceptive pill (COCP)) for 21 consecutive days, starting on the day after ellaOne intake	
Reporting group title	Placebo
Reporting group description:	
Intake of 1 pill of Placebo on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 for 21 consecutive days, starting on the day after Placebo intake	
Subject analysis set title	Full Analysis Set population
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized and treated subjects for whom at least one assessment of the main criterion (Hoogland score) is available	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized and treated subjects who completed the study without any major violations of the protocol	
Subject analysis set title	Specificity population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects of the FAS population that had a follicle size ≤18mm at time of treatment initiation	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
A ll randomized and treated subjects that have received at least one dose of the study treatment, irrespective of satisfying other criteria	

Primary: Follicle status at end of treatment period in FAS population

End point title	Follicle status at end of treatment period in FAS population
End point description:	
Quiescence was considered as reached when the Hoogland score was ≤ 3, ovulation when the score was 6. The other possible follicle status were Luteinized Unruptured Follicle (LUF) or persistent follicle.	
End point type	Primary
End point timeframe:	
Follicular growth was measured (transvaginal ultrasounds TVU) at each subject visit on site (i.e. every 2 to 3 days), up to follicular size <= 13 mm at 2 consecutive visits.	

End point values	ellaOne	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: Subjects				
Quiescence	24	23		
Ovulation	13	12		
LUF	2	1		
Persistent follicle	0	1		

Statistical analyses

Statistical analysis title	Effect of treatment - quiescence

Statistical analysis description:

Competing risk survival analysis - A Fine and Gray model was used in which treatment, dominant follicular size at inclusion, cycle day at inclusion and previous method of contraception were the explaining variables.

Comparison groups	ellaOne v Placebo
Number of subjects included in analysis	76
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.2089
Method	Competing risk analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.702
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.404
upper limit	1.219

Statistical analysis title	Effect of follicle size - quiescence

Statistical analysis description:

Competing risk survival analysis - A Fine and Gray model was used in which treatment, dominant follicular size at inclusion, cycle day at inclusion and previous method of contraception were the explaining variables.

Comparison groups	ellaOne v Placebo
Number of subjects included in analysis	76
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.0061
Method	Competing risk analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.696
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.538
upper limit	0.902

Statistical analysis title	Effect of treatment - ovulation

Statistical analysis description:

Competing risk survival analysis - A Fine and Gray model was used in which treatment, dominant follicular size at inclusion, cycle day at inclusion and previous method of contraception were the explaining variables.

Comparison groups	ellaOne v Placebo
Number of subjects included in analysis	76
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.2376
Method	Competing risk analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	1.769
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.686
upper limit	4.56

Statistical analysis title	Effect of follicle size - ovulation

Statistical analysis description:

Competing risk survival analysis - A Fine and Gray model was used in which treatment, dominant follicular size at inclusion, cycle day at inclusion and previous method of contraception were the explaining variables.

Comparison groups	ellaOne v Placebo
Number of subjects included in analysis	76
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.0024
Method	Competing risk analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.186
upper limit	2.212

Secondary: Time to quiescence in FAS population

End point title	Time to quiescence in FAS population

End point description:

Time from treatment initiation to Hoogland score ≤ 3

End point type	Secondary

End point timeframe:

Follicular growth was measured by transvaginal ultrasounds (TVU) at each subject visit on site (i.e. every 2 to 3 days), up to follicular size <= 13 mm at 2 consecutive visits; Quiescence was defined as Hoogland score (HS) <=3

End point values	ellaOne	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: percentage of subjects				
number (not applicable)				
Day 7 of COCP	70.8	60.9		
Day 14 of COCP	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ovulation in FAS population

End point title	Time to ovulation in FAS population

End point description:

Time from treatment initiation to Hoogland score = 6

End point type	Secondary

End point timeframe:

Measure of follicle growth was done at each visit on site, i.e. every 2 or 3 days.

End point values	ellaOne	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: Percentage of subjects				
number (not applicable)				
Ovulation on COCP day 4	15.4	50		
Ovulation on COCP day 6	76.9	91.7		
Ovulation on COCP day 7	76.9	100		
Ovulation on COCP day 11	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the end of study visit regardless of seriousness or relationship to investigational product. Analysis was performed on safety population.

Adverse event reporting additional description:

Headache was the most frequently reported adverse event that was judged to be possibly related to both ellaOne®/placebo and COCP intake

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	ellaOne

Reporting group description:

Intake of 1 pill of 30mg ellaOne on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 for 21 consecutive days, starting on the day after ellaOne intake

Reporting group title	Placebo

Reporting group description:

Intake of 1 pill of Placebo on the day of inclusion, followed by a daily intake of 1 tablet of Microgynon 30 for 21 consecutive days, starting on the day after Placebo intake

Serious adverse events	ellaOne	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 37 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ellaOne	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 39 (66.67%)	23 / 37 (62.16%)	
Nervous system disorders			
headache	Additional description: Headache was the most frequently reported adverse event that was judged to be possibly related to both ellaOne®/placebo and COCP intake		
subjects affected / exposed	9 / 39 (23.08%)	9 / 37 (24.32%)	
occurrences (all)	14	10	
Gastrointestinal disorders			

Abdominal pain lower	Additional description: Abdominal pain lower was the second most frequently reported adverse event that was judged to be possibly related to both ellaOne®/placebo and COCP intake		
subjects affected / exposed	6 / 39 (15.38%)	1 / 37 (2.70%)	
occurrences (all)	7	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 39 (10.26%)	5 / 37 (13.51%)	
occurrences (all)	4	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2012	This amendement was written on request of the Netherlands Ethics committe. The following updates were done: the size of each treatment arm was specified in section 'sample size justification'; The declaration of Helsinki in Appendix A was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25994664