Clinical trial results:
A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone

Summary

EudraCT number	2015-003150-40
Trial protocol	CZ HU SE FI PL DE BE
Global end of trial date	17 October 2018

Results information

Result version number	v1 (current)
This version publication date	11 May 2019
First version publication date	11 May 2019

Trial information

Trial identification

Sponsor protocol code	MIT-Es0001-C301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mithra Pharmaceuticals
Sponsor organisation address	Rue Saint Georges 5-7, Liège, Belgium, 4000
Public contact	Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals SA, +32 43492822, clinical.trials@mithra.com
Scientific contact	Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals SA, +32 43492822, clinical.trials@mithra.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	26 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2018
Global end of trial reached?	Yes
Global end of trial date	17 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the contraceptive efficacy of 15 mg estetrol (E4)/ 3 mg drospirenone (DRSP) using the Pearl Index in participants aged 18 to 35 years.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki in place at the time of study conduct. The study was conducted in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP] guideline CPMP/ICH/135/95), and compliant with the European Union Clinical Trial Directive (EU CTD): Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2016
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	Finland: 181
Country: Number of subjects enrolled	Czech Republic: 335
Country: Number of subjects enrolled	Germany: 141
Country: Number of subjects enrolled	Hungary: 190
Country: Number of subjects enrolled	Norway: 108
Country: Number of subjects enrolled	Poland: 221
Country: Number of subjects enrolled	Russian Federation: 280
Country: Number of subjects enrolled	Belgium: 87
Country: Number of subjects enrolled	Sweden: 10
Worldwide total number of subjects	1553
EEA total number of subjects	1273

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)	1553
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1,744 participants aged 18-50 years were screened. Of these, 1,577 participants were enrolled in the study: 1,373 participants aged 18 to 35 years and 204 participants aged > 35 years. Of the 1577 enrolled participants, 1553 participants were treated in the study (1,353 participants aged 18-35 years and 200 participants aged > 35 years)

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)

Arm description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population.

Arm type	Experimental
Investigational medicinal product name	15 mg estetrol/ 3 mg drospirenone
Investigational medicinal product code	E4/ DRSP
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg estetrol/ 3 mg drospirenone was administered once daily for 24 consecutive days followed by placebo once daily for 4 consecutive days.

Number of subjects in period 1	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)
Started	1553
Completed	1218
Not completed	335
Adverse event not related to bleeding	104
Consent withdrawn by subject	78
Pregnancy	7
Adverse event related to bleeding	53
Unspecified	26
Lost to follow-up	41
Pregnancy wish	15
Protocol deviation	11

Baseline characteristics

Reporting groups	
Reporting group title	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)
Reporting group description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population.	

Reporting group values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)	Total	
Number of subjects	1553	1553	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	27.1		
standard deviation	± 6.86	-	
Gender categorical			
Units: Subjects			
Female	1553	1553	
Race			
Participants who did not receive the investigational product have been disclosed as not reported			
Units: Subjects			
White	1532	1532	
Black or African American	8	8	
Asian	10	10	
Other	3	3	
Ethnicity			
Participants who did not receive the investigational product have been disclosed as not reported			
Units: Subjects			
Hispanic or Latino	13	13	
Not Hispanic or Latino	1540	1540	
Weight			
Units: kilogram(s)			
arithmetic mean	63.83		
standard deviation	± 10.53	-	
Height			
Units: cm			
arithmetic mean	166.53		
standard deviation	± 6.234	-	
BMI			
Units: kg/m^2			
arithmetic mean	23		
standard deviation	± 3.469	-	

End points

End points reporting groups

Reporting group title	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)
Reporting group description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population.	
Subject analysis set title	15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants between 18 and 35 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population.	
Subject analysis set title	Endometrial biopsy baseline results
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with an endometrial biopsy at the screening visit and visit 7a.	
Subject analysis set title	Endometrial biopsy visit 7a results
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with an endometrial biopsy at the screening visit and visit 7a.	
Subject analysis set title	Unscheduled bleeding analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with at least 1 evaluable cycle for the bleeding analysis.	
Subject analysis set title	Unscheduled spotting analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with at least 1 evaluable cycle for the bleeding analysis.	
Subject analysis set title	Q-LES-Q-SF baseline results
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline Q-LES-Q-SF results.	
Subject analysis set title	Q-LES-Q-SF end of treatment results
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment Q-LES-Q-SF results.	
Subject analysis set title	MDQ baseline results
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline MDQ results.	
Subject analysis set title	MDQ end of treatment results
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment MDQ results.

Subject analysis set title	Physical examination baseline results
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline physical examination results.

Subject analysis set title	Physical examination end of treatment results
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment physical examination results.

Subject analysis set title	Gynecological examination baseline results
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline gynecological examination results.

Subject analysis set title	Gynecological examination end of treatment results
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment gynecological examination results.

Primary: Primary Pearl Index of participants between 18 and 35 years of age

End point title	Primary Pearl Index of participants between 18 and 35 years of age[1]

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only at-risk cycles were included in the denominator of the Pearl Index calculation.
At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

End point type	Primary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

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 additional statistical analysis was planned for this endpoint.

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age)			
Subject group type	Subject analysis set			
Number of subjects analysed	1313[2]			
Units: Pearl Index				
number (confidence interval 95%)	0.47 (0.15 to 1.11)			

Notes:

[2] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Modified Pearl Index of participants between 18 and 35 years of age

End point title	Modified Pearl Index of participants between 18 and 35 years of age

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only modified at-risk cycles were included in the denominator of the Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age)			
Subject group type	Subject analysis set			
Number of subjects analysed	1343[3]			
Units: Pearl Index				
number (confidence interval 95%)	0.44 (0.14 to 1.03)			

Notes:

[3] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 modified at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Primary method failure Pearl Index of participants between 18 and 35 years of age

End point title	Primary method failure Pearl Index of participants between 18 and 35 years of age

End point description:

The method failure Pearl Index (also referred to as "perfect-use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only at-risk cycles were included in the denominator of the Pearl Index calculation.

At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age)			
Subject group type	Subject analysis set			
Number of subjects analysed	1313[4]			
Units: Method failure Pearl Index				
number (confidence interval 95%)	0.29 (0.06 to 0.83)			

Notes:

[4] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Modified method failure Pearl Index of participants between 18 and 35 years of age

End point title	Modified method failure Pearl Index of participants between 18 and 35 years of age

End point description:

The method failure Pearl Index (also referred to as "perfect use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only modified at-risk cycles were included in the denominator of the method failure Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age)			
Subject group type	Subject analysis set			
Number of subjects analysed	1343[5]			
Units: Method failure Pearl Index				
number (confidence interval 95%)	0.26 (0.05 to 0.77)			

Notes:

[5] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 modified at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative on-treatment pregnancy rate of participants between 18 and 35 years of age

End point title	Cumulative on-treatment pregnancy rate of participants between 18 and 35 years of age

End point description:

Cumulative pregnancy rate was calculated per year using life-table methods.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age)			
Subject group type	Subject analysis set			
Number of subjects analysed	1353[6]			
Units: Percent				
number (confidence interval 95%)	0.45 (0.19 to 1.09)			

Notes:

[6] - Participants aged 18 to 35 years, inclusive, at screening, who received at least one dose of IP

Statistical analyses

No statistical analyses for this end point

Secondary: Modified Pearl Index of participants between 18 and 50 years of age

End point title	Modified Pearl Index of participants between 18 and 50 years of age

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only modified at-risk cycles were included in the denominator of the Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1542[7]			
Units: Pearl Index				
number (confidence interval 95%)	0.38 (0.12 to 0.89)			

Notes:

[7] - Participants aged 18 to 50 years, inclusive, at screening with at least 1 modified at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Primary method failure Pearl Index of participants between 18 and 50 years of age

End point title	Primary method failure Pearl Index of participants between 18 and 50 years of age

End point description:

The method failure Pearl Index (also referred to as "perfect-use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only at-risk cycles were included in the denominator of the Pearl Index calculation.
At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1510[8]			
Units: Method failure Pearl Index				
number (confidence interval 95%)	0.25 (0.05 to 0.72)			

Notes:

[8] - Participants aged 18 to 50 years, inclusive, at screening with at least one at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Pearl Index of participants between 18 and 50 years of age

End point title	Primary Pearl Index of participants between 18 and 50 years of age

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only at-risk cycles were included in the denominator of the Pearl Index calculation.
At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1510[9]			
Units: Pearl Index				
number (confidence interval 95%)	0.41 (0.13 to 0.96)			

Notes:

[9] - Participants aged 18 to 50 years, inclusive, at screening with at least one at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative on-treatment pregnancy rate of participants between 18 and 50 years of age

End point title	Cumulative on-treatment pregnancy rate of participants between 18 and 50 years of age

End point description:

Cumulative pregnancy rate was calculated per year using life-table methods.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1553[10]			
Units: Percent				
number (confidence interval 95%)	0.39 (0.16 to 0.94)			

Notes:

[10] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

Statistical analyses

No statistical analyses for this end point

Secondary: Modified method failure Pearl Index of participants between 18 and 50 years of age

End point title	Modified method failure Pearl Index of participants between 18 and 50 years of age

End point description:

The method failure Pearl Index (also referred to as "perfect use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only modified at-risk cycles were included in the denominator of the method failure Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1542[11]			
Units: Method failure Pearl Index				
number (confidence interval 95%)	0.23 (0.05 to 0.67)			

Notes:

[11] - Participants aged 18 to 50 years, inclusive, at screening with at least 1 modified at-risk cycle

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants experiencing unscheduled bleeding and/ or spotting episodes per cycle

End point title	Number of participants experiencing unscheduled bleeding and/

	or spotting episodes per cycle

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1507[12]			
Units: Participants				
Cycle 1	354			
Cycle 2	282			
Cycle 3	250			
Cycle 4	249			
Cycle 5	238			
Cycle 6	207			
Cycle 7	170			
Cycle 8	202			
Cycle 9	182			
Cycle 10	168			
Cycle 11	155			
Cycle 12	154			

Notes:

[12] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of unscheduled bleeding and spotting days per cycle

End point title	Number of unscheduled bleeding and spotting days per cycle

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

End point values	Unscheduled bleeding analysis	Unscheduled spotting analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1507[13]	1507[14]		
Units: Days				
arithmetic mean (standard deviation)				
Cycle 1	0.2 (± 0.89)	0.8 (± 1.99)		
Cycle 2	0.1 (± 0.66)	0.5 (± 1.50)		
Cycle 3	0.1 (± 0.67)	0.5 (± 1.46)		
Cycle 4	0.2 (± 0.79)	0.5 (± 1.55)		
Cycle 5	0.1 (± 0.70)	0.5 (± 1.35)		
Cycle 6	0.1 (± 0.80)	0.4 (± 1.24)		
Cycle 7	0.1 (± 0.68)	0.4 (± 1.17)		
Cycle 8	0.1 (± 0.72)	0.4 (± 1.19)		
Cycle 9	0.1 (± 0.70)	0.4 (± 1.13)		
Cycle 10	0.1 (± 0.61)	0.4 (± 1.25)		
Cycle 11	0.1 (± 0.72)	0.3 (± 1.18)		
Cycle 12	0.1 (± 0.68)	0.4 (± 1.23)		

Notes:

[13] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

[14] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants not experiencing scheduled bleeding and/ or spotting per cycle

End point title	Number of participants not experiencing scheduled bleeding and/ or spotting per cycle

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1507[15]			
Units: Participants				
Cycle 1	84			
Cycle 2	90			
Cycle 3	105			
Cycle 4	83			
Cycle 5	91			
Cycle 6	91			

Cycle 7	90			
Cycle 8	103			
Cycle 9	92			
Cycle 10	89			
Cycle 11	80			
Cycle 12	94			

Notes:

[15] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of scheduled bleeding and/ or spotting days per cycle

End point title	Number of scheduled bleeding and/ or spotting days per cycle

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1507[16]			
Units: Days				
arithmetic mean (standard deviation)				
Cycle 1	6.1 (± 4.95)			
Cycle 2	5.3 (± 3.62)			
Cycle 3	5.2 (± 3.99)			
Cycle 4	5.0 (± 3.14)			
Cycle 5	4.9 (± 3.43)			
Cycle 6	4.9 (± 3.34)			
Cycle 7	4.7 (± 2.80)			
Cycle 8	4.8 (± 3.85)			
Cycle 9	4.7 (± 2.87)			
Cycle 10	4.6 (± 2.69)			
Cycle 11	4.7 (± 3.16)			
Cycle 12	4.6 (± 2.97)			

Notes:

[16] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal laboratory assessment results

End point title	Number of participants with abnormal laboratory assessment results

End point description:

End point type	Secondary

End point timeframe:

Screening to End of Treatment (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1553[17]			
Units: Participants	55			

Notes:

[17] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal vital signs

End point title	Number of participants with abnormal vital signs

End point description:

All abnormal findings in vital signs that were considered by the Investigator to be clinically significant were recorded as adverse events.

End point type	Secondary

End point timeframe:

Screening to End of Treatment (12 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1553[18]			
Units: Participants	15			

Notes:

[18] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal physical examination results

End point title	Number of participants with abnormal physical examination results

End point description:

Physical examinations included the body as a whole, skin, head (eyes, ears, nose and throat), neck, cardiovascular system, respiratory system, musculoskeletal system, neurological system, lymphatic/ thyroid system and the abdomen

End point type	Secondary

End point timeframe:

Screening to End of Treatment (12 months)

End point values	Physical examination baseline results	Physical examination end of treatment results		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1553[19]	1498[20]		
Units: Participants				
Body as a whole	5	5		
Skin	16	22		
Head, eyes, ears, nose and throat	10	3		
Neck	1	1		
Cardiovascular	0	1		
Respiratory	2	1		
Musculoskeletal	0	1		
Neurologic	0	2		
Lymphatic/Thyroid	2	1		
Abdomen	0	1		

Notes:

[19] - Participants aged 18 to 50 years, inclusive, at screening with baseline PE results

[20] - Participants aged 18 to 50 years, inclusive at screening with end of treatment PE results

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal gynecological examination results

End point title	Number of participants with abnormal gynecological examination results

End point description:

End point type	Secondary

End point timeframe:

Screening to End of Cycle 13 (12 months)

End point values	Gynecological examination baseline results	Gynecological examination end of treatment results		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1553[21]	1499[22]		
Units: Participants				
Cervix examination	21	13		
Breast examination	8	8		
Vagina examination	8	8		
Uterus examination	11	6		
Adnexa examination	4	2		
External genitalia examination	1	1		

Notes:

[21] - Participants aged 18 to 50 years, inclusive at screening with baseline gynecological results

[22] - Participants aged 18 to 50 years, inclusive at screening with end of treatment gynecological results

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing common treatment emergent adverse events related to the investigational product

End point title	Percentage of participants experiencing common treatment emergent adverse events related to the investigational product

End point description:

Common treatment emergent adverse events occur in more than 1% of trial participants.

End point type	Secondary

End point timeframe:

Day 1 to End of Treatment (13 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1553[23]			
Units: Percent of participants				
number (not applicable)				
Metrorrhagia	5.0			
Vaginal haemorrhage	4.3			
Breast pain	2.4			
Dysmenorrhoea	2.1			
Menorrhagia	1.0			
Libido decreased	2.2			
Mood altered	1.0			
Mood swings	1.0			
Acne	3.8			
Headache	2.8			

Weight increased	1.7			

Notes:

[23] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who experience at least one treatment emergent serious adverse event

End point title	Number of participants who experience at least one treatment emergent serious adverse event

End point description:

End point type	Secondary

End point timeframe:

Day 1 to End of Treatment (13 months)

End point values	15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age)			
Subject group type	Reporting group			
Number of subjects analysed	1553[24]			
Units: Participants	13			

Notes:

[24] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

Statistical analyses

No statistical analyses for this end point

Secondary: Endometrial biopsy histology at screening and end of treatment

End point title	Endometrial biopsy histology at screening and end of treatment

End point description:

End point type	Secondary

End point timeframe:

Screening to End of Cycle 13 (12 months)

End point values	Endometrial biopsy baseline results	Endometrial biopsy visit 7a results		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Percent of participants				
number (not applicable)				
Proliferative (weakly)	30	10		
Proliferative (active)	24	1		
Proliferative (disordered)	22	11		
Secretory (cyclic)	16	1		
Secretory (progestational)	6	4		
Inactive	7	61		
Atrophic	2	11		
Insufficient tissue	1	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life enjoyment and satisfaction questionnaire – short form (Q-LES-Q-SF) at screening and end of treatment

End point title	Quality of life enjoyment and satisfaction questionnaire – short form (Q-LES-Q-SF) at screening and end of treatment

End point description:

Participants were asked to rate a series of different items from 1 (very poor) to 5 (very good). The total score of the Q-LES-Q-SF was derived by summing the first 14 items to obtain the raw total score, then transformed into a percentage maximum using the following formula: (raw score – 14)/56. A positive change from baseline indicated the participant had experienced improved overall life satisfaction and contentment during the previous week.

End point type	Secondary

End point timeframe:

Day 1 to End of Treatment (12 months)

End point values	Q-LES-Q-SF baseline results	Q-LES-Q-SF end of treatment results		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1379[25]	1406[26]		
Units: Percent				
arithmetic mean (standard deviation)				
Percentage maximum	73.4 (± 12.77)	73.8 (± 12.82)		
Satisfaction with medicine	4.0 (± 0.78)	4.0 (± 0.77)		
Overall life satisfaction over the past week	4.0 (± 0.68)	4.0 (± 0.70)		

Notes:

[25] - Participants aged 18 to 50 years, inclusive, at screening with baseline Q-LES-Q-SF results

[26] - Participants aged 18 to 50 years, inclusive, at screening with end of treatment Q-LES-Q-SF

results.

Statistical analyses

No statistical analyses for this end point

Secondary: Menstrual distress questionnaire (MDQ) at screening and end of treatment

End point title	Menstrual distress questionnaire (MDQ) at screening and end of treatment

End point description:

The participant rated common symptoms and feelings associated with menstruation from 0 (no experience of symptom) to 4 (present, severe) pre-menstruation, during menstruation and after menstruation. An overall positive change from baseline represents an increase in symptom or feeling severity.

End point type	Secondary

End point timeframe:

Day 1 to End of Treatment (12 months)

End point values	MDQ baseline results	MDQ end of treatment results		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1526[27]	1412[28]		
Units: Result				
arithmetic mean (standard deviation)				
Pain (Intermenstrual)	1.8 (± 2.62)	1.6 (± 2.46)		
Pain (Premenstrual)	2.8 (± 3.01)	2.6 (± 3.09)		
Pain (Menstrual)	4.0 (± 3.71)	3.5 (± 3.73)		
Water retention (Intermenstrual)	1.0 (± 1.73)	1.0 (± 1.69)		
Water retention (Premenstrual)	2.2 (± 2.45)	2.1 (± 2.44)		
Water retention (Menstrual)	2.2 (± 2.47)	2.1 (± 2.55)		
Autonomic reactions (Intermenstrual)	0.4 (± 1.08)	0.3 (± 1.02)		
Autonomic reactions (Premenstrual)	0.5 (± 1.18)	0.4 (± 1.11)		
Autonomic reactions (Menstrual)	0.7 (± 1.41)	0.5 (± 1.32)		
Negative affect (Intermenstrual)	2.0 (± 3.66)	1.8 (± 3.62)		
Negative affect (Premenstrual)	3.9 (± 4.90)	3.5 (± 4.80)		
Negative affect (Menstrual)	3.9 (± 4.89)	3.5 (± 4.84)		
Impaired concentration (Intermenstrual)	1.1 (± 2.25)	1.0 (± 2.13)		
Impaired concentration (Premenstrual)	1.4 (± 2.60)	1.3 (± 2.50)		
Impaired concentration (Menstrual)	1.4 (± 2.63)	1.4 (± 2.69)		
Behaviour change (Intermenstrual)	0.9 (± 1.90)	0.9 (± 1.83)		
Behaviour change (Premenstrual)	1.5 (± 2.40)	1.4 (± 2.34)		
Behaviour change (Menstrual)	1.9 (± 2.86)	1.7 (± 2.73)		
Arousal (Intermenstrual)	3.7 (± 4.22)	3.4 (± 3.88)		
Arousal (Premenstrual)	3.3 (± 3.80)	3.0 (± 3.57)		

Arousal (Menstrual)	3.2 (± 3.68)	2.9 (± 3.43)		
Control (Intermenstrual)	0.5 (± 1.38)	0.5 (± 1.37)		
Control (Premenstrual)	0.6 (± 1.47)	0.5 (± 1.36)		
Control (Menstrual)	0.6 (± 1.41)	0.6 (± 1.42)		

Notes:

[27] - Participants aged 18 to 50 years, inclusive, at screening, with baseline MDQ results

[28] - Participants aged 18 to 50 years, inclusive, at screening, with end of treatment MDQ results

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening to End of Treatment (13 months)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Overall Study
Reporting group description: Participants aged 18 to 50 years, inclusive, at screening	

Serious adverse events	Overall Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 1553 (0.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Spinal column injury			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine without aura			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 1553 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 1553 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	784 / 1553 (50.48%)		
Investigations			
Low density lipoprotein increased			
subjects affected / exposed	18 / 1553 (1.16%)		
occurrences (all)	19		
Weight increased			
subjects affected / exposed	36 / 1553 (2.32%)		
occurrences (all)	36		
Nervous system disorders			
Headache			
subjects affected / exposed	120 / 1553 (7.73%)		
occurrences (all)	171		
Dizziness			
subjects affected / exposed	19 / 1553 (1.22%)		
occurrences (all)	24		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	74 / 1553 (4.76%)		
occurrences (all)	151		
Dysmenorrhoea			

subjects affected / exposed occurrences (all) Metrorrhagia subjects affected / exposed occurrences (all) Menorrhagia subjects affected / exposed occurrences (all) Breast pain subjects affected / exposed occurrences (all) Vaginal discharge subjects affected / exposed occurrences (all)	47 / 1553 (3.03%) 74 85 / 1553 (5.47%) 156 15 / 1553 (0.97%) 17 42 / 1553 (2.70%) 51 16 / 1553 (1.03%) 19		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 25 / 1553 (1.61%) 45 36 / 1553 (2.32%) 48 27 / 1553 (1.74%) 49 20 / 1553 (1.29%) 25		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 15 / 1553 (0.97%) 16		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 65 / 1553 (4.19%) 69		
Psychiatric disorders			

Mood altered			
subjects affected / exposed	19 / 1553 (1.22%)		
occurrences (all)	19		
Libido decreased			
subjects affected / exposed	38 / 1553 (2.45%)		
occurrences (all)	43		
Mood swings			
subjects affected / exposed	18 / 1553 (1.16%)		
occurrences (all)	18		
Irritability			
subjects affected / exposed	18 / 1553 (1.16%)		
occurrences (all)	18		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	19 / 1553 (1.22%)		
occurrences (all)	20		
Infections and infestations			
Tonsillitis			
subjects affected / exposed	29 / 1553 (1.87%)		
occurrences (all)	31		
Nasopharyngitis			
subjects affected / exposed	52 / 1553 (3.35%)		
occurrences (all)	63		
Vulvovaginal mycotic infection			
subjects affected / exposed	17 / 1553 (1.09%)		
occurrences (all)	22		
Urinary tract infection			
subjects affected / exposed	30 / 1553 (1.93%)		
occurrences (all)	35		
Bronchitis			
subjects affected / exposed	15 / 1553 (0.97%)		
occurrences (all)	16		
Influenza			
subjects affected / exposed	28 / 1553 (1.80%)		
occurrences (all)	30		
Vaginal infection			

subjects affected / exposed	29 / 1553 (1.87%)		
occurrences (all)	33		
Sinusitis			
subjects affected / exposed	17 / 1553 (1.09%)		
occurrences (all)	19		
Respiratory tract infection			
subjects affected / exposed	18 / 1553 (1.16%)		
occurrences (all)	19		
Cystitis			
subjects affected / exposed	24 / 1553 (1.55%)		
occurrences (all)	29		
Vulvovaginal candidiasis			
subjects affected / exposed	20 / 1553 (1.29%)		
occurrences (all)	23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2016	- In line with the urgent safety memo issued on 04 August 2016, the requirement to use condoms for the first 7 days after switching from an intrauterine or dermally implantable contraceptive was added to the instructions for starting the first pack of tablets.
06 February 2017	- "Nicotine-containing products" was added to the exclusion criteria #7 to clarify that this criterion includes cigarettes, e-cigarettes and cigars but not marijuana. - Instructions for the participant to contact the site immediately if the participant decided to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site in order to minimize the likelihood of the participant discontinuing study product use without notifying the Investigator. This allowed alternative contraception to be instituted if desired and a discontinuation visit to be scheduled. - Clarification was added for participants participating in the Endometrial Safety Sub-study (Finland, Germany, and Poland only) and desiring to discontinue the study. In that case, the second biopsy planned at Visit 7a could be done for participants who discontinue after the completion of the 10th treatment cycle and if she was still under treatment i.e., Cycle 11 or 12. - Clarification was added to describe how to handle scheduling the Early Termination Visit for a subject, whether or not she had started study product, who desired early discontinuation from the study. - Clarification was added that the information about pregnancy follow-up applied to all enrolled participants who started study product. In the rare circumstance that an enrolled participant became pregnant and claimed she never started study product, the pregnancy did not have to be followed if she could prove she never started study product by returning all of the study product she had received. - Text regarding the withdrawal of participants was modified to clarify that any participant who underwent Visit 2 and was withdrawn from the study prior or after the investigational product intake should have participated in an Early Termination Visit and should have been immediately counseled about alternative contraception.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported