Clinical trial results:
A Single-center, Randomized, Open-label, Two-arm Study to Evaluate the Ovarian Function Inhibition of a Monophasic Combined Oral Contraceptive (COC) Containing 15 mg Estetrol (E4) and 3 mg Drospirenone (DRSP) and a Monophasic COC Containing 20mcg Ethinylestradiol (EE)/3 mg DRSP (YAZ®), Administered Orally Once Daily in a 24/4 Day Regimen for Three Consecutive Cycles

Summary

EudraCT number	2016-004267-40
Trial protocol	NL
Global end of trial date	07 June 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	MIT-Es0001-C202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03091595
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	07 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2018
Global end of trial reached?	Yes
Global end of trial date	07 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of the 15 mg estetrol (E4)/3 mg drospirenone (DRSP) combination and the 20 mcg ethinylestradiol (EE)/3 mg DRSP used as reference combination on ovarian function inhibition at Treatment Cycle 1 and Treatment Cycle 3

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 Council for 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: Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 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	Netherlands: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	82
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were stratified by day of ovulation in the Pre-Treatment Cycle and Body Mass Index. Each participant completed a Screening Visit, a Pre-Treatment Cycle followed by 3 treatment cycles, a Post-Treatment Cycle and a Follow-Up Visit. In case of use of hormonal contraception, at least 1 wash-out cycle was performed prior to treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	15 mg estetrol/3 mg drospirenone

Arm description:

15 mg E4 combined with 3 mg DRSP administered in a 24/4-day regimen. One tablet per day orally for 3 consecutive treatment cycles.

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 E4 combined with 3 mg DRSP administered in a 24/4-day regimen (i.e. 24 days of active tablets followed by 4 days of placebo tablets). One tablet per day orally for 3 treatment cycles.

Arm title	20 mcg ethinylestradiol/3 mg drospirenone

Arm description:

20 mcg EE combined with 3 mg DRSP administered in a 24/4-day regimen. One tablet per day orally for 3 consecutive treatment cycles.

Arm type	Active comparator
Investigational medicinal product name	Yaz®
Investigational medicinal product code	EE/DRSP
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20 mcg EE combined with 3 mg DRSP (Yaz®) administered in a 24/4-day regimen (i.e. 24 days of active tablets followed by 4 days of placebo tablets). One tablet per day orally for 3 treatment cycles.

Number of subjects in period 1	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol/3 mg drospirenone
Started	41	41
Completed	37	34
Not completed	4	7
Adverse event not related to bleeding	1	2
Other	1	4
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	15 mg estetrol/3 mg drospirenone
Reporting group description:	
15 mg E4 combined with 3 mg DRSP administered in a 24/4-day regimen. One tablet per day orally for 3 consecutive treatment cycles.	
Reporting group title	20 mcg ethinylestradiol/3 mg drospirenone
Reporting group description:	
20 mcg EE combined with 3 mg DRSP administered in a 24/4-day regimen. One tablet per day orally for 3 consecutive treatment cycles.	

Reporting group values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol/3 mg drospirenone	Total
Number of subjects	41	41	82
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
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	41	82
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	25.5	25.7	
standard deviation	± 4.52	± 3.93	-
Gender categorical Units: Subjects			
Female	41	41	82
Male	0	0	0
Race Units: Subjects			
Asian	1	2	3
Black or African American	1	2	3
Other	2	2	4
White	37	35	72
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	41	39	80
Stratum Units: Subjects			
BMI ≤30.0 kg/m2 - Ovulation < Day 12	2	2	4

BMI ≤30.0 kg/m2 - Ovulation < Day 15	7	6	13
BMI ≤30.0 kg/m2 - Ovulation < Day 18	16	16	32
BMI ≤30.0 kg/m2 - Ovulation < Day 21	10	10	20
BMI ≤30.0 kg/m2 - Ovulation < Day 24	3	2	5
BMI ≤30.0 kg/m2 - Ovulation < Day 27	3	2	5
BMI >30 kg/m2 - Ovulation < Day 15	0	1	1
BMI >30 kg/m2 - Ovulation < Day 21	0	1	1
BMI >30 kg/m2 - Ovulation < Day 24	0	1	1
Weight			
Units: Kilograms			
arithmetic mean	66.49	67.33	
standard deviation	± 9.024	± 12.357	-
Height			
Units: Centimetres			
arithmetic mean	171.2	169.2	
standard deviation	± 7.22	± 7.13	-
Body Mass Index			
Units: Kilogram/metre^2			
arithmetic mean	22.66	23.49	
standard deviation	± 2.474	± 4.089	-

End points

End points reporting groups

Reporting group title	15 mg estetrol/3 mg drospirenone
Reporting group description:	
15 mg E4 combined with 3 mg DRSP administered in a 24/4-day regimen. One tablet per day orally for 3 consecutive treatment cycles.	
Reporting group title	20 mcg ethinylestradiol/3 mg drospirenone
Reporting group description:	
20 mcg EE combined with 3 mg DRSP administered in a 24/4-day regimen. One tablet per day orally for 3 consecutive treatment cycles.	

Primary: Number of Participants with Ovarian Inhibition at Treatment Cycle 1

End point title	Number of Participants with Ovarian Inhibition at Treatment Cycle 1[1]
End point description:	
Ovulation inhibition was assessed by rating the suppression of the ovaries using the Hoogland score. This score is based on the follicle sizes assessed by transvaginal ultrasonography (TVUS) and the estradiol (E2) and progesterone levels during a pill cycle. The scores range between 1 and 6, with overall ovarian function inhibition indicated by a Hoogland score of less than 4.	
End point type	Primary
End point timeframe:	
Cycle 1 Day 3 to Day 27	

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	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[2]	41[3]		
Units: Participants				
1: No Activity	34	34		
2: Potential Activity	3	4		
3: Non-Active Follicle Like Structure (FLS)	1	0		
4: Active FLS	2	2		
5: Luteinized Unruptured Follicle (LUF)	0	0		
6: Ovulation	0	1		

Notes:

[2] - This total is inclusive of participants with analysable results at Treatment Cycle 1.

[3] - This total is inclusive of participants with analysable results at Treatment Cycle 1.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Ovarian Inhibition at Treatment Cycle 3

End point title	Number of Participants with Ovarian Inhibition at Treatment

	Cycle 3[4]

End point description:

Ovulation inhibition was assessed by rating the suppression of the ovaries using the Hoogland score. This score is based on the follicle sizes assessed by TVUS and the E2 and progesterone levels during a pill cycle. The scores range between 1 and 6, with overall ovarian function inhibition indicated by a Hoogland score of less than 4.

End point type	Primary

End point timeframe:

Cycle 3 Day 3 to Day 27

Notes:

[4] - 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	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[5]	37[6]		
Units: Participants				
1: No Activity	25	31		
2: Potential Activity	4	3		
3: Non-Active Follicle Like Structure (FLS)	1	0		
4: Active FLS	8	2		
5: Luteinized Unruptured Follicle (LUF)	0	0		
6: Ovulation	0	1		

Notes:

[5] - This total is inclusive of participants with analysable results at Treatment Cycle 3.

[6] - This total is inclusive of participants with analysable results at Treatment Cycle 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Level of Luteinizing Hormone (LH)

End point title	Serum Level of Luteinizing Hormone (LH)

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 40 participants had available data. In the 20 mcg EE/3 mg DRSP arm, up to 41 participants had available data.

End point type	Secondary

End point timeframe:

Day 3, 6, 9, 12, 15, 18, 21, 24, 27 of Treatment Cycle 1 and Treatment Cycle 3 and on Day 3 of the Treatment Cycle 2

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[7]	41[8]		
Units: mU/mL				
arithmetic mean (standard deviation)				
Cycle 1: Day 03	6.10 (± 2.325)	5.15 (± 1.949)		
Cycle 1: Day 06	6.54 (± 3.465)	5.32 (± 2.144)		
Cycle 1: Day 09	6.18 (± 3.722)	4.91 (± 2.573)		
Cycle 1: Day 12	5.90 (± 3.493)	4.43 (± 2.765)		
Cycle 1: Day 15	5.90 (± 3.230)	3.72 (± 2.821)		
Cycle 1: Day 18	5.21 (± 2.999)	3.18 (± 3.380)		
Cycle 1: Day 21	4.83 (± 2.845)	2.96 (± 3.580)		
Cycle 1: Day 24	5.32 (± 3.528)	2.48 (± 2.859)		
Cycle 1: Day 27	6.16 (± 3.406)	3.96 (± 3.059)		
Cycle 2: Day 03	6.64 (± 3.358)	5.26 (± 2.928)		
Cycle 3: Day 03	6.71 (± 3.025)	4.66 (± 3.283)		
Cycle 3: Day 06	7.22 (± 3.638)	4.75 (± 3.474)		
Cycle 3: Day 09	6.88 (± 4.140)	4.43 (± 4.798)		
Cycle 3: Day 12	6.21 (± 3.714)	2.72 (± 2.884)		
Cycle 3: Day 15	6.29 (± 3.676)	2.46 (± 2.796)		
Cycle 3: Day 18	5.86 (± 3.300)	1.95 (± 2.431)		
Cycle 3: Day 21	5.78 (± 3.281)	2.11 (± 2.393)		
Cycle 3: Day 24	5.64 (± 3.386)	1.84 (± 2.267)		
Cycle 3: Day 27	6.50 (± 3.251)	3.03 (± 3.028)		

Notes:

[7] - This total is inclusive of participants with analysable results at Day 3 of the Treatment Cycle 1.

[8] - This total is inclusive of participants with analysable results at Day 3 of the Treatment Cycle 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Level of Follicle Stimulating Hormone (FSH)

End point title	Serum Level of Follicle Stimulating Hormone (FSH)

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 40 participants had available data. In the 20 mcg EE/3 mg DRSP arm, up to 41 participants had available data.

End point type	Secondary

End point timeframe:

Day 3, 6, 9, 12, 15, 18, 21, 24, 27 of Treatment Cycle 1 and Treatment Cycle 3 and on Day 3 of Treatment Cycle 2

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[9]	41[10]		
Units: mU/mL				
arithmetic mean (standard deviation)				
Cycle 1: Day 03	5.19 (± 1.438)	4.86 (± 1.619)		
Cycle 1: Day 06	5.31 (± 1.915)	4.77 (± 1.623)		
Cycle 1: Day 09	4.81 (± 1.887)	4.31 (± 1.556)		
Cycle 1: Day 12	4.68 (± 1.744)	3.63 (± 1.425)		
Cycle 1: Day 15	4.67 (± 1.922)	3.26 (± 1.911)		
Cycle 1: Day 18	4.50 (± 1.926)	2.71 (± 1.735)		
Cycle 1: Day 21	4.33 (± 1.744)	2.46 (± 1.825)		
Cycle 1: Day 24	4.66 (± 2.045)	2.43 (± 1.756)		
Cycle 1: Day 27	6.37 (± 2.149)	4.96 (± 3.016)		
Cycle 2: Day 03	5.72 (± 1.511)	4.86 (± 1.606)		
Cycle 3: Day 03	5.45 (± 1.495)	4.61 (± 1.437)		
Cycle 3: Day 06	5.27 (± 1.522)	4.00 (± 1.716)		
Cycle 3: Day 09	4.94 (± 1.958)	3.16 (± 1.842)		
Cycle 3: Day 12	4.83 (± 1.922)	2.23 (± 1.468)		
Cycle 3: Day 15	4.62 (± 1.813)	1.95 (± 1.500)		
Cycle 3: Day 18	4.50 (± 1.677)	1.70 (± 1.520)		
Cycle 3: Day 21	4.53 (± 1.766)	1.85 (± 1.761)		
Cycle 3: Day 24	4.48 (± 1.900)	1.86 (± 2.041)		
Cycle 3: Day 27	6.52 (± 2.273)	3.70 (± 2.931)		

Notes:

[9] - This includes all participants with analysable results at Day 3 of the Treatment Cycle 1.

[10] - This includes all participants with analysable results at Day 3 of the Treatment Cycle 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Level of Estradiol (E2)

End point title	Serum Level of Estradiol (E2)

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 40 participants had available data. In the 20 mcg EE/3 mg DRSP arm, up to 41 participants had available data.

End point type	Secondary

End point timeframe:

Day 3, 6, 9, 12, 15, 18, 21, 24, 27 of Treatment Cycle 1 and Treatment Cycle 3 and on Day 3 of Treatment Cycle 2

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[11]	41[12]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1: Day 03	19.303 (± 18.7648)	13.325 (± 6.1189)		
Cycle 1: Day 06	16.588 (± 21.3997)	12.981 (± 15.2934)		
Cycle 1: Day 09	8.672 (± 6.6284)	16.678 (± 31.2045)		
Cycle 1: Day 12	8.196 (± 7.3155)	18.916 (± 47.7497)		
Cycle 1: Day 15	7.818 (± 6.2617)	13.454 (± 35.2221)		
Cycle 1: Day 18	10.125 (± 14.0052)	12.375 (± 39.9830)		
Cycle 1: Day 21	8.329 (± 8.4955)	9.893 (± 25.9804)		
Cycle 1: Day 24	8.819 (± 9.9171)	9.409 (± 21.0308)		
Cycle 1: Day 27	21.281 (± 24.7604)	35.233 (± 44.3946)		
Cycle 2: Day 03	32.471 (± 75.3828)	34.338 (± 71.8123)		
Cycle 3: Day 03	29.149 (± 45.5948)	16.805 (± 27.4196)		
Cycle 3: Day 06	26.947 (± 44.3196)	24.732 (± 65.3223)		
Cycle 3: Day 09	23.664 (± 43.6809)	29.548 (± 89.5314)		
Cycle 3: Day 12	22.382 (± 48.7051)	27.450 (± 97.9313)		
Cycle 3: Day 15	15.865 (± 27.8212)	23.165 (± 80.2365)		
Cycle 3: Day 18	12.574 (± 22.9375)	20.682 (± 62.6405)		
Cycle 3: Day 21	12.339 (± 19.0090)	19.666 (± 67.1126)		
Cycle 3: Day 24	8.910 (± 8.6778)	8.678 (± 22.5650)		
Cycle 3: Day 27	21.080 (± 19.1215)	23.489 (± 46.2374)		

Notes:

[11] - This includes all participants with analysable results at Day 3 of the Treatment Cycle 1.

[12] - This includes all participants with analysable results at Day 3 of the Treatment Cycle 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Level of Progesterone (P)

End point title	Serum Level of Progesterone (P)

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 40 participants had available data. In the 20 mcg EE/3 mg DRSP arm, up to 41 participants had available data.

End point type	Secondary

End point timeframe:

Day 3, 6, 9, 12, 15, 18, 21, 24, 27 of Treatment Cycle 1 and Treatment Cycle 3 and on Day 3 of Treatment Cycle 2

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[13]	41[14]		
Units: nmol/L				
arithmetic mean (standard deviation)				
Cycle 1: Day 03	1.140 (± 0.5528)	0.810 (± 0.5416)		
Cycle 1: Day 06	0.984 (± 0.6870)	0.779 (± 0.5250)		
Cycle 1: Day 09	0.958 (± 0.6145)	0.790 (± 0.5667)		
Cycle 1: Day 12	0.906 (± 0.9826)	0.789 (± 0.4851)		
Cycle 1: Day 15	1.016 (± 0.7504)	1.145 (± 2.5358)		
Cycle 1: Day 18	1.026 (± 1.0024)	0.759 (± 0.5109)		
Cycle 1: Day 21	0.884 (± 0.6721)	0.808 (± 0.4573)		
Cycle 1: Day 24	0.934 (± 0.7628)	1.571 (± 4.9825)		
Cycle 1: Day 27	0.790 (± 0.6245)	1.163 (± 2.3064)		
Cycle 2: Day 03	0.822 (± 0.5094)	0.695 (± 0.4436)		
Cycle 3: Day 03	0.942 (± 0.5983)	0.654 (± 0.4404)		
Cycle 3: Day 06	0.999 (± 0.6775)	0.716 (± 0.4357)		
Cycle 3: Day 09	0.844 (± 0.5113)	1.094 (± 1.6176)		
Cycle 3: Day 12	0.719 (± 0.3951)	0.790 (± 0.5358)		
Cycle 3: Day 15	0.791 (± 0.4282)	0.826 (± 0.5984)		
Cycle 3: Day 18	0.787 (± 0.4776)	0.814 (± 0.8053)		
Cycle 3: Day 21	0.948 (± 0.5949)	0.886 (± 0.7359)		
Cycle 3: Day 24	0.878 (± 0.6476)	0.861 (± 0.5419)		
Cycle 3: Day 27	0.888 (± 0.7096)	0.913 (± 0.6235)		

Notes:

[13] - This includes all participants with analysable results at Day 3 of the Treatment Cycle 1.

[14] - This includes all participants with analysable results at Day 3 of the Treatment Cycle 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Endometrial Thickness

End point title	Maximum Endometrial Thickness

End point description:

Endometrial thickness will be measured using TVUS. Maximum endometrial thickness was defined as the largest endometrial thickness during a cycle.

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 40 participants had available data. In the 20 mcg EE/3 mg DRSP arm, up to 41 participants had available data.

End point type	Secondary

End point timeframe:

Pre-Treatment and Day 3 (±1) to Day 27 (±1) of each Cycle

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[15]	41[16]		
Units: Millimetres				
arithmetic mean (standard deviation)				
Pre-Treatment Cycle	9.28 (± 2.158)	9.38 (± 2.028)		
Cycle 1	6.16 (± 1.482)	6.43 (± 2.164)		
Cycle 2	4.43 (± 1.360)	4.33 (± 1.794)		
Cycle 3	6.21 (± 1.617)	5.85 (± 1.545)		
Post-Treatment Cycle	9.22 (± 2.002)	9.14 (± 2.406)		

Notes:

[15] - This includes all participants with analysable results at Pre-Treatment Cycle.

[16] - This includes all participants with analysable results at Pre-Treatment Cycle.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Diameter of the Largest Follicle

End point title	Mean Diameter of the Largest Follicle

End point description:

Return to fertility will be measured by monitoring follicular growth using TVUS and confirmed by serum progesterone.

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 38 participants had available data. On Day 24 in the 15 mg E4/3 mg DRSP arm, no participants has available data as there were no measurements taken after ovulation. In the 20 mcg EE/3 mg DRSP arm, up to 37 participants had available data. N/A results are indicated by '99999'.

End point type	Secondary

End point timeframe:

Day 3 to Day 24 of Post-Treatment Cycle

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[17]	37[18]		
Units: Millimeters				
arithmetic mean (standard deviation)				
Day 03	9.90 (± 3.518)	9.57 (± 5.214)		
Day 06	12.63 (± 3.380)	11.66 (± 4.938)		
Day 09	14.86 (± 3.773)	13.42 (± 3.614)		
Day 12	15.04 (± 5.683)	16.74 (± 3.565)		
Day 15	11.55 (± 5.220)	17.31 (± 5.955)		
Day 18	14.09 (± 6.781)	12.09 (± 6.683)		
Day 21	9.00 (± 2.115)	14.31 (± 8.162)		
Day 24	99999 (± 99999)	11.15 (± 3.889)		

Notes:

[17] - This includes all participants with analysable results at Day 3 of the Post-Treatment Cycle.

[18] - This includes all participants with analysable results at Day 3 of the Post-Treatment Cycle.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience at Least One Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Participants who Experience at Least One Treatment-Emergent Adverse Event (TEAE)

End point description:

A treatment-emergent AE (TEAE) is defined as any event not present prior to the first administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

End point type	Secondary

End point timeframe:

Day 1 to Follow-Up Visit (+ 30 days)

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[19]	41[20]		
Units: Participants	38	37		

Notes:

[19] - This analysis includes all participants who received at least one dose of study medication.

[20] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience Pregnancy During Treatment

End point title	Number of Participants who Experience Pregnancy During Treatment

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to Follow-Up Visit (+ 30 days)

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[21]	41[22]		
Units: Participants	0	0		

Notes:

[21] - This analysis includes all participants who received at least one dose of study medication.

[22] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience a Clinically Significant Change in Physical Examination Results

End point title	Number of Participants who Experience a Clinically Significant Change in Physical Examination Results

End point description:

Physical examination included

- Eyes, ears, nose, throat, including thyroid and neck
- Respiratory system
- Cardiovascular system
- Peripheral vascular system
- Gastrointestinal system, including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymphatic nodes
- BMI

End point type	Secondary

End point timeframe:

Day 1 to End of Follow-Up Visit (+ 30 Days)

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[23]	41[24]		
Units: Participants	0	0		

Notes:

[23] - This analysis includes all participants who received at least one dose of study medication.

[24] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience a Clinically Significant Change in Gynecological Examination Results

End point title	Number of Participants who Experience a Clinically Significant Change in Gynecological Examination Results

End point description:

Gynecological examination included:

- Inspection of outer genital region
- Inspection of vagina and cervix
- Examination of uterus and adnexa by TVUS
- Breast examination (clinical)

End point type	Secondary

End point timeframe:

Day 1 to End of Follow-Up Visit (+ 30 Days)

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[25]	41[26]		
Units: Participants	0	0		

Notes:

[25] - This analysis includes all participants who received at least one dose of study medication.

[26] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience a Clinically Significant Change in Clinical Laboratory Results

End point title	Number of Participants who Experience a Clinically Significant Change in Clinical Laboratory Results

End point description:

End point type	Secondary

End point timeframe:

Day 1 to End of Follow-Up Visit (+ 30 Days)

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[27]	41[28]		
Units: Participants	0	0		

Notes:

[27] - This analysis includes all participants who received at least one dose of study medication.

[28] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience a Clinically Significant Change in Electrocardiogram (ECG) Results

End point title	Number of Participants who Experience a Clinically Significant Change in Electrocardiogram (ECG) Results

End point description:

Standard 12-lead ECG machines were used.

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 3

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[29]	41[30]		
Units: Participants	0	0		

Notes:

[29] - This analysis includes all participants who received at least one dose of study medication.

[30] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experience a Clinically Significant Change in Echocardiogram Results

End point title	Number of Participants who Experience a Clinically Significant Change in Echocardiogram Results

End point description:

End point type	Secondary

End point timeframe:

Day 1 to End of Cycle 3 (Day 28)

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[31]	41[32]		
Units: Participants	0	0		

Notes:

[31] - This analysis includes all participants who received at least one dose of study medication.

[32] - This analysis includes all participants who received at least one dose of study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Diastolic Blood Pressure

End point title	Change from Baseline in Diastolic Blood Pressure

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, up to 41 participants had available data. In the 20 mcg EE/3 mg DRSP arm, up to 40 participants had available data.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3 and Follow-up Visit

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[33]	39[34]		
Units: mmHg				
arithmetic mean (standard deviation)				
Cycle 1	-0.8 (± 6.37)	-1.3 (± 5.79)		
Cycle 2	-0.7 (± 6.30)	-0.9 (± 6.25)		
Cycle 3	0.4 (± 6.24)	-0.6 (± 5.87)		
Follow-up	-1.8 (± 8.25)	0.1 (± 5.99)		

Notes:

[33] - This includes all participants who received at least one dose of study drug with results at Cycle 1.

[34] - This includes all participants who received at least one dose of study drug with results at Cycle 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Systolic Blood Pressure

End point title	Change from Baseline in Systolic Blood Pressure

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, 41 to 37 participants had available data. In the 20 mcg EE/3 mg DRSP arm, 40 to 37 participants had available data.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3 and Follow-up Visit

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[35]	39[36]		
Units: mmHg				
arithmetic mean (standard deviation)				
Cycle 1	0.6 (± 8.29)	-1.7 (± 6.16)		
Cycle 2	-1.6 (± 10.81)	-1.8 (± 7.13)		
Cycle 3	0.3 (± 7.38)	-2.7 (± 7.10)		
Follow-up	2.8 (± 8.59)	3.3 (± 7.36)		

Notes:

[35] - This includes all participants who received at least one dose of study drug with results at Cycle 1.

[36] - This includes all participants who received at least one dose of study drug with results at Cycle 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pulse Rate

End point title	Change from Baseline in Pulse Rate

End point description:

The participants with available data varied at each specified time point. In the 15 mg E4/3 mg DRSP arm, 37 to 41 participants had available data. In the 20 mcg EE/3 mg DRSP arm, 37 to 40 participants had available data.

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3 and Follow-up Visit

End point values	15 mg estetrol/3 mg drospirenone	20 mcg ethinylestradiol /3 mg drospirenone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[37]	39[38]		
Units: Beats/min				
arithmetic mean (standard deviation)				
Cycle 1	-0.3 (± 11.14)	-0.6 (± 11.17)		

Cycle 2	0.9 (± 11.63)	-0.5 (± 10.21)		
Cycle 3	2.8 (± 12.66)	1.6 (± 9.93)		
Follow-up	0.6 (± 10.63)	1.8 (± 10.09)		

Notes:

[37] - This includes all participants who received at least one dose of study drug with results at Cycle 1.

[38] - This includes all participants who received at least one dose of study drug with results at Cycle 1.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to End of Follow-Up Visit (+30 days)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	20 mcg EE/3 mg DRSP
Reporting group description: -	
Reporting group title	15 mg E4/3 mg DRSP
Reporting group description: -	

Serious adverse events	20 mcg EE/3 mg DRSP	15 mg E4/3 mg DRSP	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (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: 5 %

Non-serious adverse events	20 mcg EE/3 mg DRSP	15 mg E4/3 mg DRSP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 41 (90.24%)	38 / 41 (92.68%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Surgical and medical procedures			
Dental care			
subjects affected / exposed	0 / 41 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Nervous system disorders			
Headache			

subjects affected / exposed	14 / 41 (34.15%)	12 / 41 (29.27%)	
occurrences (all)	24	26	
Dizziness			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 41 (9.76%)	3 / 41 (7.32%)	
occurrences (all)	4	3	
Malaise			
subjects affected / exposed	4 / 41 (9.76%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	9 / 41 (21.95%)	9 / 41 (21.95%)	
occurrences (all)	12	10	
Nausea			
subjects affected / exposed	9 / 41 (21.95%)	6 / 41 (14.63%)	
occurrences (all)	10	6	
Diarrhoea			
subjects affected / exposed	3 / 41 (7.32%)	6 / 41 (14.63%)	
occurrences (all)	3	9	
Vomiting			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	6 / 41 (14.63%)	13 / 41 (31.71%)	
occurrences (all)	8	22	
Breast enlargement			
subjects affected / exposed	1 / 41 (2.44%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
Dysmenorrhoea			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal			

disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 41 (9.76%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
Cough			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Eczema			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	
occurrences (all)	6	1	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	3 / 41 (7.32%)	5 / 41 (12.20%)	
occurrences (all)	3	6	
Mood swings			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 41 (9.76%)	5 / 41 (12.20%)	
occurrences (all)	4	7	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	12 / 41 (29.27%)	16 / 41 (39.02%)	
occurrences (all)	14	19	
Influenza			
subjects affected / exposed	7 / 41 (17.07%)	11 / 41 (26.83%)	
occurrences (all)	8	11	
Gastroenteritis			
subjects affected / exposed	3 / 41 (7.32%)	3 / 41 (7.32%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2017	Protocol Version 2.0 The changes introduced were items observed during preparation of the study. • Update of signatories and addition of contact details of additional laboratories. • Clarification of the timing of clinical laboratory assessments at early-termination visit. • Clarification of Exclusion Criteria #37 and #41.
09 March 2017	Protocol Version 3.0 The changes introduced were: • Clarification of Inclusion Criterion #5 where only routine clinical laboratory should be considered. • Clarification of the reference to routine clinical laboratory and cardiac markers where applicable. • Administrative change was made to the signatories.
22 November 2017	Protocol Version 4.0 The laboratory for routine clinical safety laboratory was changed from QPS Holdings, LLC to Analytical Biochemical Laboratory BV.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported