Clinical trial results:
A Randomized Double-blind Placebo Controlled Phase 3 Trial to evaluate the Efficacy and Safety of Estetrol for the Treatment of Moderate to Severe Vasomotor Symptoms in Postmenopausal Women (E4Comfort Study I)

Summary

EudraCT number	2019-001289-14
Trial protocol	PL GB SK HU LT CZ ES IT RO
Global end of trial date	08 February 2024

Results information

Result version number	v1 (current)
This version publication date	23 February 2025
First version publication date	23 February 2025

Trial information

Trial identification

Sponsor protocol code	MIT-Do001-C301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04209543
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Estetra SRL
Sponsor organisation address	Rue Saint-Georges 5, Liege, Belgium, 4000
Public contact	Clinical Study Leader, Estetra SRL, clinical.trials@estetra.com
Scientific contact	Clinical Study Leader, Estetra SRL, clinical.trials@estetra.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	08 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Arms 1-3:
Efficacy Study Part: measure the effect of treatment with estetrol (E4) 15 mg or E4 20 mg compared with placebo, regarding the frequency and severity of moderate to severe vasomotor symptoms (VMS) in postmenopausal women at 4 and 12 weeks. This part of the study included non-hysterectomized and hysterectomized women.

Arm 4:
Safety Study Part: assess the effect of treatment with E4 20 mg + Progesterone (P4) 100 mg on the endometrium. This part of the study included non-hysterectomized women only.

Protection of trial subjects:

The study was conducted according to the clinical study protocol, according with the principles of the Declaration of Helsinki, and local regulations, as well as according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH/CPMP/135/95).

Adverse events (AEs) and vital signs were recorded at all visits (from screening onward). Based on the medical opinion of the investigator, all new clinically relevant abnormalities or significant changes at the study visits were reported as AEs in the electronic case report form (eCRF). All safety assessments were performed according to accepted methods.

All non-hysterectomized subjects received treatment with P4 200 mg once daily for 14 consecutive days after completion of treatment with E4/Placebo.

An independent data safety monitoring board (DSMB) was involved in overseeing general and endometrial safety data of the study at regular, pre-defined intervals. The DSMB made recommendations regarding continuation, modification, or termination of the study. The DSMB was supported by a Clinical Event Committee, that was responsible for adjudicating cardiovascular and thrombotic events.

Background therapy:

None.

Evidence for comparator:

Not applicable.

DEFINITIONS USED IN THIS DATA RECORD:

ITT (Intent-to-Treat Set): included all randomized subjects who received at least one dose of randomized study drug. Used as the primary analysis population for the efficacy analyses. All analyses on this set were based on randomized treatment.

SAF (Safety Analysis Set): included all (randomized*) subjects who received at least one dose of (randomized*) study drug. Used for all analyses of safety, tolerability and background characteristics. All analyses on this set were based on treatment received.
(*) Efficacy Study Part only.

Endometrial Safety Analysis Set: included all subjects who received at least one dose of study drug and had an evaluable biopsy at Baseline and at Month 12 (defined by a Visit window as on or after Day 326) or had a diagnosis of endometrial hyperplasia prior to Month 12. Evaluable biopsies included all biopsies,

except for biopsies with no tissue or insufficient tissue. This analysis set was defined only for the Safety Study Part.

ABBREVIATIONS

Hx, hysterectomized
NH, non-hysterectomized

Actual start date of recruitment	17 December 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 168
Country: Number of subjects enrolled	Russian Federation: 47
Country: Number of subjects enrolled	Brazil: 290
Country: Number of subjects enrolled	Argentina: 44
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	Poland: 495
Country: Number of subjects enrolled	Romania: 87
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	United Kingdom: 119
Country: Number of subjects enrolled	Czechia: 168
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Lithuania: 23
Worldwide total number of subjects	1562
EEA total number of subjects	852

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)	1551
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Postmenopausal women aged 40-65 y seeking treatment for the relief of VMS associated with menopause (N=4502) were screened according to study inclusion and exclusion criteria:
-Efficacy Study Part: >=7 moderate to severe VMS/day or >=50 moderate to severe VMS/week.
-Safety Study Part: non hysterectomized; >=1 moderate to severe VMS/week.

Pre-assignment

Screening details:

Screening visit was generally up to 4 weeks before the first administration of the study drug. Screening was done according to the study inclusion and exclusion criteria. Signed Informed Consent Form was obtained prior to any study-related procedures.

Period 1

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

Blinding implementation details:

Efficacy Study Part (ESP, Arms 1, 2, 3): randomized, double blind;
Safety Study Part (SSP, Arm 4): open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	E4 15 mg

Arm description:

Efficacy Study Part: randomized, double-blind.
Estetrol monohydrate 15 mg (E4 15 mg), equivalent to estetrol 14.2 mg.
The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

Arm type	Experimental
Investigational medicinal product name	Estetrol monohydrate
Investigational medicinal product code	
Other name	E4 15 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Efficacy Study Part: randomized, double-blind.
Estetrol monohydrate 15 mg (E4 15 mg), equivalent to estetrol 14.2 mg.
The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

Arm title	E4 20 mg

Arm description:

Efficacy Study Part: randomized, double-blind.
Estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg.
The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

Arm type	Experimental

Investigational medicinal product name	Estetrol monohydrate
Investigational medicinal product code	
Other name	E4 20 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Efficacy Study Part: randomized, double-blind.
Estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg.
The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

Arm title	Placebo

Arm description:

Efficacy Study Part: randomized, double-blind.
Placebo, film-coated tablet, with no active substance.
The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

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:

Efficacy Study Part: randomized, double-blind.
Film coated tablet, with no active substance.
The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

Arm title	E4 20 mg + P4 100 mg

Arm description:

Safety Study Part: open-label.
All subjects received estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg) continuously, once a day, for up to 53 weeks.

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

Dosage and administration details:

Safety Study part: open-label arm.
All subjects received E4 20 mg, equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg).
The study drugs were to be taken once a day for up to 53 weeks, at approximately the same time each day.

Investigational medicinal product name	Estetrol monohydrate
Investigational medicinal product code	
Other name	E4 20 mg
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Safety Study Part: open-label arm.
All subjects received E4 20 mg, equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg) continuously for up to 53 weeks.
The study drugs were to be taken once a day for up to 53 weeks, at approximately the same time each day.

Number of subjects in period 1	E4 15 mg	E4 20 mg	Placebo
Started	213	213	214
Completed	166	164	174
Not completed	47	49	40
Consent withdrawn by subject	15	13	9
Physician decision	-	-	-
Adverse event, non-fatal	11	9	4
Other	3	4	5
Death - Covid-19	1	-	-
Endometrial Biopsy With Proliferative Disorder	5	2	-
Adverse events - Serious	-	3	1
Covid-19	-	-	3
Lost to follow-up	5	4	4
Sponsor decision	-	-	2
Lack of efficacy	4	3	6
Protocol deviation	3	11	6

Number of subjects in period 1	E4 20 mg + P4 100 mg
Started	922
Completed	402
Not completed	520
Consent withdrawn by subject	154
Physician decision	37
Adverse event, non-fatal	220
Other	21
Death - Covid-19	-
Endometrial Biopsy With Proliferative Disorder	-
Adverse events - Serious	18
Covid-19	7
Lost to follow-up	33
Sponsor decision	2
Lack of efficacy	6
Protocol deviation	22

Baseline characteristics

Reporting groups	
Reporting group title	E4 15 mg
Reporting group description:	
Efficacy Study Part: randomized, double-blind. Estetrol monohydrate 15 mg (E4 15 mg), equivalent to estetrol 14.2 mg. The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.	
Reporting group title	E4 20 mg
Reporting group description:	
Efficacy Study Part: randomized, double-blind. Estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg. The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.	
Reporting group title	Placebo
Reporting group description:	
Efficacy Study Part: randomized, double-blind. Placebo, film-coated tablet, with no active substance. The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.	
Reporting group title	E4 20 mg + P4 100 mg
Reporting group description:	
Safety Study Part: open-label. All subjects received estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg) continuously, once a day, for up to 53 weeks.	

Reporting group values	E4 15 mg	E4 20 mg	Placebo
Number of subjects	213	213	214
Age categorical Units: Subjects			
18-64 years	209	213	211
65-84 years	4	0	3
Age continuous Units: years			
arithmetic mean	53.6	53.8	54.4
standard deviation	± 4.47	± 4.83	± 5.25
Gender categorical Units: Subjects			
Female	213	213	214
Male	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	3	2
Black or African American	17	11	12
Native Hawaiian or Other Pacific Islander	0	0	0
White	185	194	192
Other	10	5	8
Ethnic Origin Units: Subjects			

Hispanic/Latino	68	61	44
Not Hispanic/Latino	145	152	170
Missing	0	0	0
Smoking habit Units: Subjects			
Yes	26	20	25
No	179	187	180
Missing	8	6	9
Hysterectomy status Units: Subjects			
Hysterectomized	110	110	110
Non Hysterectomized	103	103	104
Subject had a Bilateral Oophorectomy Units: Subjects			
Yes	47	53	45
No	165	160	169
Missing	1	0	0
Frequency of Moderate to Severe VMS			
Weekly frequency of moderate to severe vasomotor symptoms (VMS) at baseline is defined as the sum of all recorded moderate to severe VMS experienced between Day -7 and Day --1 of the study. VMS severity rating scale: Mild = sensation of heat without sweating. Moderate = sensation of heat with sweating. Allows continuation of activity. Severe = sensation of heat with sweating. Causes cessation of activity. Number of subjects with data for this characteristic: Hx E4 15 mg N=106 NH E4 15 mg N=103 Hx E4 20 mg N=109 NH E4 20 mg N=103 Hx Placebo N=108 NH Placebo N=104 Arm 4 N=777			
Units: Number of Moderate to Severe VMS			
arithmetic mean	78.94	83.81	75.49
standard deviation	± 37.580	± 51.183	± 34.666
Body mass index (BMI) Units: kg/m^2			
arithmetic mean	27.32	27.42	27.71
standard deviation	± 4.319	± 4.194	± 4.651

Reporting group values	E4 20 mg + P4 100 mg	Total	
Number of subjects	922	1562	
Age categorical Units: Subjects			
18-64 years	918	1551	
65-84 years	4	11	
Age continuous Units: years			
arithmetic mean	53.9		
standard deviation	± 4.76	-	

Gender categorical Units: Subjects			
Female	922	1562	
Male	0	0	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	2	8	
Black or African American	43	83	
Native Hawaiian or Other Pacific Islander	0	0	
White	843	1414	
Other	33	56	
Ethnic Origin Units: Subjects			
Hispanic/Latino	198	371	
Not Hispanic/Latino	722	1189	
Missing	2	2	
Smoking habit Units: Subjects			
Yes	135	206	
No	786	1332	
Missing	1	24	
Hysterectomy status Units: Subjects			
Hysterectomized	0	330	
Non Hysterectomized	922	1232	
Subject had a Bilateral Oophorectomy Units: Subjects			
Yes	8	153	
No	914	1408	
Missing	0	1	
Frequency of Moderate to Severe VMS			
Weekly frequency of moderate to severe vasomotor symptoms (VMS) at baseline is defined as the sum of all recorded moderate to severe VMS experienced between Day -7 and Day --1 of the study. VMS severity rating scale: Mild = sensation of heat without sweating. Moderate = sensation of heat with sweating. Allows continuation of activity. Severe = sensation of heat with sweating. Causes cessation of activity. Number of subjects with data for this characteristic: Hx E4 15 mg N=106 NH E4 15 mg N=103 Hx E4 20 mg N=109 NH E4 20 mg N=103 Hx Placebo N=108 NH Placebo N=104 Arm 4 N=777			
Units: Number of Moderate to Severe VMS			
arithmetic mean	29.88		
standard deviation	± 29.545	-	
Body mass index (BMI) Units: kg/m^2			
arithmetic mean	26.77		

standard deviation	± 4.183	-	

End points

End points reporting groups

Reporting group title	E4 15 mg
Reporting group description:	
Efficacy Study Part: randomized, double-blind. Estetrol monohydrate 15 mg (E4 15 mg), equivalent to estetrol 14.2 mg. The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.	
Reporting group title	E4 20 mg
Reporting group description:	
Efficacy Study Part: randomized, double-blind. Estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg. The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.	
Reporting group title	Placebo
Reporting group description:	
Efficacy Study Part: randomized, double-blind. Placebo, film-coated tablet, with no active substance. The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.	
Reporting group title	E4 20 mg + P4 100 mg
Reporting group description:	
Safety Study Part: open-label. All subjects received estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg) continuously, once a day, for up to 53 weeks.	
Subject analysis set title	E4 15 mg Hysterectomized
Subject analysis set type	Safety analysis
Subject analysis set description:	
E4 15 mg Hysterectomized	
Subject analysis set title	E4 15 mg Non-Hysterectomized
Subject analysis set type	Safety analysis
Subject analysis set description:	
Non-Hysterectomized E4 15 mg	
Subject analysis set title	E4 20 mg Hysterectomized
Subject analysis set type	Safety analysis
Subject analysis set description:	
E4 20 mg Hysterectomized	
Subject analysis set title	E4 20 mg Non-Hysterectomized
Subject analysis set type	Safety analysis
Subject analysis set description:	
E4 20 mg Non-Hysterectomized	
Subject analysis set title	Placebo Hysterectomized
Subject analysis set type	Safety analysis
Subject analysis set description:	
Placebo Hysterectomized	
Subject analysis set title	Placebo Non-Hysterectomized
Subject analysis set type	Safety analysis
Subject analysis set description:	
Placebo Non-Hysterectomized	

Primary: 1_Mean change in weekly frequency of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 4 -- Efficacy Study Part

End point title	1_Mean change in weekly frequency of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 4 -- Efficacy Study Part[1]

End point description:

Efficacy Study Part
The weekly frequency of moderate to severe VMS at baseline is defined as the sum of all recorded moderate to severe VMS experienced during the last 7 consecutive days prior randomization.
The weekly frequency of moderate to severe VMS at Week 4 is defined as the sum of all recorded moderate to severe VMS experienced during Week 4.
(VMS=vasomotor symptoms)

End point type	Primary

End point timeframe:

Week 0 (Baseline), Week 4.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193[2]	195[3]	200[4]	
Units: number of moderate to severe VMS				
arithmetic mean (confidence interval 95%)	-40.65 (-46.44 to -34.86)	-51.75 (-58.46 to -45.04)	-30.42 (-35.23 to -25.60)	

Notes:

[2] - ITT

[3] - ITT

[4] - ITT

Statistical analyses

Statistical analysis title	Week 4; E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-9.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.81
upper limit	-0.45

Statistical analysis title	Week 4; E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-14.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.85
upper limit	-6.04

Primary: 2_Mean change in weekly frequency of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 12 -- Efficacy Study Part

End point title	2_Mean change in weekly frequency of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 12 -- Efficacy Study Part[5]

End point description:

Efficacy Study Part
The weekly frequency of moderate to severe VMS at baseline is defined as the sum of all recorded moderate to severe VMS experienced during the last 7 consecutive days prior randomization.
The weekly frequency of moderate to severe VMS at Week 12 is defined as the sum of all recorded moderate to severe VMS experienced during Week 12.
(VMS=vasomotor symptoms)

End point type	Primary

End point timeframe:

Week 0 (Baseline), Week 12.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[6]	161[7]	167[8]	
Units: number of moderate to severe VMS				
arithmetic mean (confidence interval 95%)	-55.96 (-62.08 to -49.84)	-70.71 (-79.24 to -62.18)	-42.17 (-48.11 to -36.23)	

Notes:

[6] - ITT

[7] - ITT

[8] - ITT

Statistical analyses

Statistical analysis title	Week 12; E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-16.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.95
upper limit	-6.87

Statistical analysis title	Week 12; E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-22.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.79
upper limit	-13.19

Primary: 3_Mean change in severity of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 4 -- Efficacy Study Part

End point title	3_Mean change in severity of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 4 -- Efficacy Study Part[9]

End point description:

Efficacy Study Part
The mean severity score of VMS at Baseline is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during the last 7 days prior randomization.
The mean severity score of VMS at Week 4 is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during Week 4.
(VMS=vasomotor symptoms)

Daily severity score of VMS = [(2 x number of moderate VMS) + (3 x number of severe VMS)]/ (total number of moderate + severe VMS), if at least one moderate to severe VMS was recorded during the day. In case of documented absence of moderate to severe VMS during the day, the daily severity was set to zero.

Severity score is derived as follows: mild = 1, moderate = 2, severe = 3.

Results are shown as change in mean severity score.

End point type	Primary

End point timeframe:

Week 0 (Baseline) and Week 4.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193[10]	195[11]	200[12]	
Units: severity score				
arithmetic mean (confidence interval 95%)	-0.61 (-0.73 to -0.49)	-0.65 (-0.78 to -0.52)	-0.32 (-0.42 to -0.23)	

Notes:

[10] - ITT

[11] - ITT

[12] - ITT

Statistical analyses

Statistical analysis title	Week 4; E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0109
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.05

Statistical analysis title	Week 4; E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.08

Primary: 4_Mean change in severity of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 12 -- Efficacy Study Part

End point title	4_Mean change in severity of moderate to severe vasomotor symptoms (VMS) from Baseline to Week 12 -- Efficacy Study Part[13]

End point description:

Efficacy Study Part
The mean severity score of VMS at Baseline is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during the last 7 days prior randomization.
The mean severity score of VMS at Week 12 is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during Week 12.
(VMS=vasomotor symptoms)

Daily severity score of VMS = [(2 x number of moderate VMS) + (3 x number of severe VMS)]/ (total number of moderate + severe VMS), if at least one moderate to severe VMS was recorded during the day. In case of documented absence of moderate to severe VMS during the day, the daily severity was set to zero.

Severity score is derived as follows: mild = 1, moderate = 2, severe = 3.

Results are shown as change in mean severity score.

End point type	Primary

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[14]	161[15]	167[16]	
Units: severity score				
arithmetic mean (confidence interval 95%)	-1.20 (-1.36 to -1.03)	-1.34 (-1.50 to -1.18)	-0.65 (-0.80 to -0.51)	

Notes:

[14] - ITT

[15] - ITT

[16] - ITT

Statistical analyses

Statistical analysis title	Week 12; E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.31

Statistical analysis title	Week 12; E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model for Repeated Measures
Parameter estimate	Least square mean difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.43

Primary: 5_Incidence (number) of endometrial hyperplasia with up to 12 months of treatment based on endometrial biopsies -- Safety Study Part

End point title	5_Incidence (number) of endometrial hyperplasia with up to 12 months of treatment based on endometrial biopsies -- Safety Study Part[17][18]

End point description:

Safety Study Part
A summary of the Final/Consensus diagnosis of endometrial biopsies across all post-baseline visits is provided.
An endometrial biopsy was obtained during the Screening period and at the EOT/Early Discontinuation visit. An additional unscheduled biopsy could have been taken if a subject presented with endometrial thickness >10 mm on TVUS, or persistent and/or recurrent bleeding. Biopsies were read by a panel of 3 independent expert pathologists as per regulatory requirements. The Final/Consensus diagnosis was defined as the concurrence of at least 2 diagnoses from the 3 pathologists, and if there was no agreement among at least 2 pathologists, the most severe pathologic diagnosis was used. The WHO classification which separates endometrial diagnoses into 6 categories (benign endometrium, simple hyperplasia, complex hyperplasia, simple atypical hyperplasia, complex atypical hyperplasia, carcinoma) was applied for the assessment of the Final/Consensus diagnosis.

End point type	Primary

End point timeframe:

Week 0 (Baseline) and Week 55 (Follow-Up).

Notes:

[17] - 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: The Safety Study Part is single arm.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Safety Study Part, which is single arm (Arm 4).

End point values	E4 20 mg + P4 100 mg			
Subject group type	Reporting group			
Number of subjects analysed	325[19]			
Units: subjects				
Benign Endometrium	324			
Simple Hyperplasia Without Atypia	0			
Complex Hyperplasia Without Atypia	1			
Simple Hyperplasia With Atypia	0			
Complex Hyperplasia With Atypia	0			
Carcinoma	0			

Notes:

[19] - No. of subjects in the Endometrial Safety Analysis Set with an available Final/Consensus Diagnosis

Statistical analyses

No statistical analyses for this end point

Primary: 6_Incidence (percentage) of endometrial hyperplasia with up to 12 months of treatment based on endometrial biopsies -- Safety Study Part

End point title	6_Incidence (percentage) of endometrial hyperplasia with up to 12 months of treatment based on endometrial biopsies -- Safety Study Part[20][21]

End point description:

Safety Study Part
Incidence (percentage (95% CI)) of endometrial hyperplasia with up to 12 months of treatment based on endometrial biopsies. The denominator for the computation of percentages and 95% CIs is the number of subjects in the Endometrial Safety Analysis Set with an available Final/Consensus Diagnosis. For details, refer to the description text of the previous endpoint.

End point type	Primary

End point timeframe:

Week 0 (Baseline) and Week 55 (Follow-Up).

Notes:

[20] - 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: The Safety Study Part is single arm.

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Safety Study Part, which is single arm (Arm 4).

End point values	E4 20 mg + P4 100 mg			
Subject group type	Reporting group			
Number of subjects analysed	325[22]			
Units: percentage				
number (confidence interval 95%)				
Benign Endometrium	99.7 (98.3 to 100.0)			
Simple Hyperplasia Without Atypia	0 (0.0 to 1.1)			
Complex Hyperplasia Without Atypia	0.3 (0.0 to 1.7)			
Simple Hyperplasia With Atypia	0 (0.0 to 1.1)			
Complex Hyperplasia With Atypia	0 (0.0 to 1.1)			
Carcinoma	0 (0.0 to 1.1)			

Notes:

[22] - No. of subjects in the Endometrial Safety Analysis Set with an available Final/Consensus Diagnosis

Statistical analyses

No statistical analyses for this end point

Secondary: 7_Proportion of Subjects with 50% and 75% Reduction in Frequency of VMS from Baseline -- Efficacy Study Part

End point title	7_Proportion of Subjects with 50% and 75% Reduction in Frequency of VMS from Baseline -- Efficacy Study Part[23]

End point description:

Efficacy Study Part
The percentage of subjects with >=50% and >=75% reduction in frequency of moderate to severe VMS from Baseline is presented for each treatment group.

End point type	Secondary

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[24]	161[25]	167[26]	
Units: percentage of subjects				
number (not applicable)				
>=50%	82.5	87.0	60.5	
>=75%	63.3	74.5	39.5	

Notes:

[24] - ITT

[25] - ITT

[26] - ITT

Statistical analyses

Statistical analysis title	1_50% at week 12, E4 15 mg vs placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	22.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	31.5

Statistical analysis title	2_50% at week 12, E4 20 mg vs placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	26.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.4
upper limit	35.5

Statistical analysis title	3_75% at week 12, E4 15 mg vs placebo
Comparison groups	Placebo v E4 15 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.3
upper limit	34.2

Statistical analysis title	4_75% at week 12, E4 20 mg vs placebo
Comparison groups	E4 20 mg v Placebo

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	35
Confidence interval	
level	95 %
sides	2-sided
lower limit	25
upper limit	45

Secondary: 8_Percentage of subjects with a clinically important difference (CID) compared to Baseline, Week 4 -- Efficacy Study Part

End point title	8_Percentage of subjects with a clinically important difference (CID) compared to Baseline, Week 4 -- Efficacy Study Part[27]

End point description:

Efficacy Study Part
Percentage of subjects with a CID compared to Baseline in the weekly frequency of moderate to severe VMS at Week 4 using the Clinical Global Impression (CGI) questionnaire.
CGI questionnaire: questionnaire in which subjects were to answer the question "Rate the total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to your condition at administration to the study, how much has it changed?". The options were: very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse.
CID (=Clinically Important Difference) = much improved + very much improved;
MCID (=Minimally Clinically Important Difference) = minimally improved.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	189[28]	184[29]	190[30]	
Units: percentage of subjects				
number (not applicable)				
CID	52.9	59.8	27.9	
MCID	34.9	28.8	39.5	
Worsen/No Change	12.2	11.4	32.6	

Notes:

[28] - ITT

[29] - ITT

[30] - ITT

Statistical analyses

Statistical analysis title	1_Week 4, CID, E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.5
upper limit	34.6

Statistical analysis title	2_Week 4, CID, E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	31.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.4
upper limit	41.4

Statistical analysis title	3_Week 4, MCID, E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3592
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	5.2

Statistical analysis title	4_Week 4, MCID, E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0297
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	-1.1

Statistical analysis title	5_Week 4, Worsen/No change, E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-20.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.6
upper limit	-12.3

Statistical analysis title	6_Week 4, Worsen/No change, E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-21.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.3
upper limit	-13.1

Secondary: 9_Percentage of subjects with a clinically important difference (CID) compared to baseline, Week 12 -- Efficacy Study Part

End point title	9_Percentage of subjects with a clinically important difference (CID) compared to baseline, Week 12 -- Efficacy Study Part[31]

End point description:

Efficacy Study Part
Percentage of subjects with a CID compared to Baseline in the weekly frequency of moderate to severe VMS at Week 12 using the Clinical Global Impression (CGI) questionnaire.
CGI questionnaire, CID, MCID: see description above.

End point type	Secondary

End point timeframe:

Week 12.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165[32]	158[33]	166[34]	
Units: percentage of subjects				
number (not applicable)				
CID	73.3	77.8	47.0	
MCID	20.0	14.6	27.7	
Worsen/No Change	6.7	7.6	25.3	

Notes:

[32] - ITT

[33] - ITT

[34] - ITT

Statistical analyses

Statistical analysis title	1_Week 12, CID, E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	26.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.2
upper limit	36.5

Statistical analysis title	2_Week 12, CID, E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.9
upper limit	40.8

Statistical analysis title	3_Week 12, MCID, E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0999
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.9
upper limit	1.4

Statistical analysis title	4_Week 12, MCID, E4 20 mg vs Placebo
Comparison groups	E4 20 mg v Placebo

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.9
upper limit	-4.4

Statistical analysis title	5_Week 12, Worsen/No change, E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.3
upper limit	-11

Statistical analysis title	6_Week 12, Worsen/No change, E4 20 mg v Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.5
upper limit	-9.9

Secondary: 10_Change from Baseline to Week 12 in VVA symptoms (subject self-

assessment) using VVA questionnaire -- Efficacy Study Part

End point title	10_Change from Baseline to Week 12 in VVA symptoms (subject self-assessment) using VVA questionnaire -- Efficacy Study Part[35]

End point description:

Efficacy Study Part
Change from Baseline to Week 12 in VVA symptoms (subject self-assessment) using VVA questionnaire.

Vulvovaginal atrophy (VVA) questionnaire and scoring system: questionnaire about the following symptoms: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. All symptoms except vaginal bleeding associated with sexual activity were graded by the subject using the following scale: 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Vaginal bleeding associated with sexual activity was documented as [0] absent or [1] present.

The proportion of subjects with vaginal bleeding associated with sexual activity was low in the E4 treatment arms and placebo at Baseline so that no reliable conclusions could be drawn.

Dyspareunia=Vaginal Pain Associated with Sexual Activity

End point type	Secondary

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163[36]	158[37]	158[38]	
Units: score				
arithmetic mean (confidence interval 95%)				
Vaginal Dryness	-0.8 (-0.9 to -0.6)	-0.6 (-0.7 to -0.4)	-0.4 (-0.5 to -0.2)	
Vaginal and/or Vulvar Irritation/Itching	-0.3 (-0.5 to -0.1)	-0.3 (-0.5 to -0.2)	-0.3 (-0.5 to -0.2)	
Dysuria	-0.2 (-0.3 to -0.1)	-0.2 (-0.3 to -0.1)	-0.2 (-0.3 to -0.1)	
Dyspareunia	-0.7 (-0.9 to -0.5)	-0.4 (-0.6 to -0.3)	-0.3 (-0.5 to -0.2)	

Notes:

[36] - ITT

N=162 for Vaginal and/or Vulvar Irritation/Itching
[37] - ITT

N=159 Vaginal and/or Vulvar Irritation/Itching
[38] - ITT

N=160 Vaginal and/or Vulvar Irritation/Itching;
N=160 Dysuria

Statistical analyses

Statistical analysis title	1_Week 12, Vaginal Dryness, E4 15 mg vs Placebo

Statistical analysis description:

Model-Adjusted Change from Baseline vs. Placebo

Comparison groups	E4 15 mg v Placebo

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.09

Statistical analysis title	2_Week 12, Vaginal Dryness, E4 20 mg vs Placebo
Statistical analysis description:	
Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1067
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.03

Statistical analysis title	3_Week 12, Vaginal/Vulvar Irr, E4 15 mg vs Placebo
Statistical analysis description:	
Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6868
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.26

Statistical analysis title	4_Week 12, Vaginal/Vulvar Irr, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	Placebo v E4 20 mg
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9757
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.21

Statistical analysis title	5_Week 12, Dysuria, E4 15 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1983
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.2

Statistical analysis title	6_Week 12, Dysuria, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 20 mg v Placebo

Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5349
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.16

Statistical analysis title	7_Week 12, Dyspareunia, E4 15 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0142
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.04

Statistical analysis title	8_Week 12, Dyspareunia, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5313
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.1

Secondary: 11_Change from Baseline to Week 12 in HRQoL using the Menopause-specific Quality of Life (MENQOL) questionnaire -- Efficacy Study Part

End point title	11_Change from Baseline to Week 12 in HRQoL using the Menopause-specific Quality of Life (MENQOL) questionnaire -- Efficacy Study Part[39]

End point description:

Efficacy Study Part
Change from Baseline to Week 12 in HRQoL using the MENQOL questionnaire.
The MENQOL questionnaire is a 29-item (Q1-Q29) assessment of quality of life designed to capture self-reported information on the presence and bother of symptoms, feelings and experiences in the domains of vasomotor, psychosocial, physical and sexual functioning, among midlife women in the immediate post-menopause period. Lower scores indicate better quality of life. The MENQOL questionnaire administered after study drug administration refers to the symptoms experienced over the past month. (HRQoL=Health-Related Quality of Life; MENQOL=Menopause-specific Quality of Life)

End point type	Secondary

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[40]	161[41]	169[42]	
Units: score				
arithmetic mean (confidence interval 95%)				
Vasomotor Domain	-3.72 (-4.04 to -3.41)	-3.71 (-4.02 to -3.39)	-2.23 (-2.58 to -1.89)	
Psychosocial Domain	-1.79 (-2.07 to -1.52)	-1.87 (-2.15 to -1.59)	-1.32 (-1.57 to -1.07)	
Physical Domain	-1.55 (-1.78 to -1.32)	-1.49 (-1.72 to -1.27)	-1.15 (-1.36 to -0.93)	
Sexual functioning Domain	-1.81 (-2.13 to -1.49)	-1.91 (-2.26 to -1.56)	-1.01 (-1.29 to -0.73)	
Total MENQOL	-2.22 (-2.44 to -2.01)	-2.25 (-2.48 to -2.01)	-1.43 (-1.63 to -1.22)	

Notes:

[40] - ITT

[41] - ITT

N=160 for Vasomotor Domain Score
[42] - ITT

Statistical analyses

Statistical analysis title	1_Week12, Vasomotor Domain, E4 15 mg vs Placebo

Statistical analysis description:

Model-Adjusted Change from Baseline vs. Placebo

Comparison groups	E4 15 mg v Placebo

Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	-0.87

Statistical analysis title	2_Week12, Vasomotor Domain, E4 20 mg vs Placebo
Statistical analysis description:	
Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	Placebo v E4 20 mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	-0.78

Statistical analysis title	3_Week12, Psychosocial Domain, E4 15 mg vs Placebo
Statistical analysis description:	
Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.17

Statistical analysis title	4_Week12, Psychosocial Domain, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.25

Statistical analysis title	5_Week12, Physical Domain, E4 15 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0728
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.02

Statistical analysis title	6_Week12, Physical Domain, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	Placebo v E4 20 mg

Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0479
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0

Statistical analysis title	7_Week12, Sexual funct Domain, E4 15 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	-0.21

Statistical analysis title	8_Week12, Sexual funct Domain, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.22

Statistical analysis title	9_Week12, Total MENQOL, E4 15 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.4

Statistical analysis title	10_Week12, Total MENQOL, E4 20 mg vs Placebo
Statistical analysis description: Model-Adjusted Change from Baseline vs. Placebo	
Comparison groups	E4 20 mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.41

Secondary: 12_Number of subjects in the different endometrial categories -- Efficacy Study Part

End point title	12_Number of subjects in the different endometrial categories -- Efficacy Study Part[43]

End point description:

Efficacy Study Part
A summary of the Final/Consensus diagnosis of endometrial biopsies across all post-baseline visits is provided.
An endometrial biopsy was obtained during the Screening period and at the EOT/Early Discontinuation visit. An additional unscheduled biopsy could have been taken if a subject presented with endometrial thickness >10 mm on TVUS, or persistent and/or recurrent bleeding. Biopsies were read by a panel of 3

independent expert pathologists as per regulatory requirements. The Final/Consensus diagnosis was defined as the concurrence of at least 2 diagnoses from the 3 pathologists, and if there was no agreement among at least 2 pathologists, the most severe pathologic diagnosis was used. The WHO classification which separates endometrial diagnoses into 6 categories (benign endometrium, simple hyperplasia, complex hyperplasia, simple atypical hyperplasia, complex atypical hyperplasia, carcinoma) was applied for the assessment of the Final/Consensus diagnosis.

End point type	Secondary

End point timeframe:

Week 0 (Baseline) and Week 15 (Follow-Up).

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Secondary study endpoint; no statistics presented.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67[44]	62[45]	56[46]	
Units: subjects				
Benign Endometrium	65	59	56	
Simple Hyperplasia Without Atypia	1	3	0	
Complex Hyperplasia Without Atypia	1	0	0	
Simple hyperplasia with atypia	0	0	0	
Complex hyperplasia with atypia	0	0	0	
Carcinoma	0	0	0	

Notes:

[44] - SAF
N=74 with performed post-baseline biopsy
N=67 with evaluable post-baseline biopsy
[45] - SAF
N=66 with performed post-baseline biopsy
N=62 with evaluable post-baseline biopsy
[46] - SAF
N=67 with performed post-baseline biopsy
N=56 with evaluable post-baseline biopsy

Statistical analyses

No statistical analyses for this end point

Secondary: 13_Percentage of subjects in the different endometrial categories -- Efficacy Study Part

End point title	13_Percentage of subjects in the different endometrial categories -- Efficacy Study Part

End point description:

Efficacy Study Part
The percentage (95% CI) of subjects in the different endometrial categories is presented. The denominator for the computation of percentages and 95% CIs is the number of subjects with an evaluable post-baseline biopsy in the SAF.
For details, refer to the description text of the previous endpoint.

End point type	Secondary

End point timeframe:

Week 0 (Baseline) and Week 15 (Follow-Up).

End point values	E4 15 mg Non-Hysterectomized	E4 20 mg Non-Hysterectomized	Placebo Non-Hysterectomized	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	67[47]	62[48]	56[49]	
Units: percentage				
number (confidence interval 95%)				
Benign Endometrium	97.0 (89.6 to 99.6)	95.2 (86.5 to 99.0)	100.0 (93.6 to 100.0)	
Simple Hyperplasia Without Atypia	1.5 (0.0 to 8.0)	4.8 (1.0 to 13.5)	0 (0.0 to 6.4)	
Complex Hyperplasia Without Atypia	1.5 (0.0 to 8.0)	0 (0.0 to 5.8)	0 (0.0 to 6.4)	
Simple Hyperplasia With Atypia	0 (0.0 to 5.4)	0 (0.0 to 5.8)	0 (0.0 to 6.4)	
Complex Hyperplasia With Atypia	0 (0.0 to 5.4)	0 (0.0 to 5.8)	0 (0.0 to 6.4)	
Carcinoma	0 (0.0 to 5.4)	0 (0.0 to 5.8)	0 (0.0 to 6.4)	

Notes:

[47] - Number of subjects with evaluable post-baseline biopsy in the SAF.

[48] - Number of subjects with evaluable post-baseline biopsy in the SAF.

[49] - Number of subjects with evaluable post-baseline biopsy in the SAF.

Statistical analyses

No statistical analyses for this end point

Secondary: 14_Frequency of vaginal bleeding and/or spotting by cycle -- Efficacy Study Part

End point title	14_Frequency of vaginal bleeding and/or spotting by cycle -- Efficacy Study Part[50]

End point description:

Efficacy Study Part
Frequency (percentage) of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on data in the patient diary.
The number of non-hysterectomized subjects with available bleeding information in diaries during the cycle is shown for each cycle under the results table.

End point type	Secondary

End point timeframe:

Cycle 1 to Cycle 4.

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Secondary study endpoint; no statistics presented.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103[51]	103[52]	104[53]	
Units: percentage of subjects				
number (not applicable)				
Cycle 1	10.5	9.4	6.2	
Cycle 2	39.6	40.4	1.1	
Cycle 3	66.3	67.5	4.5	
Cycle 4	34.4	40.8	4.8	

Notes:

[51] - SAF
Cycle 1: N=95
Cycle 2: N=91
Cycle 3: N=83
Cycle 4: N=61
[52] - SAF
Cycle 1: N=96
Cycle 2: N=89
Cycle 3: N=83
Cycle 4: N=49
[53] - SAF
Cycle 1: N=97
Cycle 2: N=93
Cycle 3: N=88
Cycle 4: N=62

Statistical analyses

No statistical analyses for this end point

Secondary: 15_Number of days with bleeding and/or spotting during each cycle -- Efficacy Study Part

End point title	15_Number of days with bleeding and/or spotting during each cycle -- Efficacy Study Part[54]

End point description:

Efficacy Study Part
Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on data in the patient diary.
The number of non-hysterectomized subjects with vaginal bleeding and/or spotting is shown for each cycle under the results table.

End point type	Secondary

End point timeframe:

Cycle 1 to Cycle 4.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Secondary study endpoint; no statistics presented.

End point values	E4 15 mg	E4 20 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103[55]	103[56]	104[57]	
Units: days				
arithmetic mean (standard deviation)				
Cycle 1	2.7 (± 1.77)	5.7 (± 7.16)	4.8 (± 2.71)	
Cycle 2	6.5 (± 5.97)	7.2 (± 4.94)	1.0 (± 0.00)	
Cycle 3	9.7 (± 7.09)	9.4 (± 6.65)	2.5 (± 1.29)	
Cycle 4	4.0 (± 2.16)	3.8 (± 2.24)	1.0 (± 0.00)	

Notes:

[55] - SAF
Cycle 1: N=10
Cycle 2: N=36
Cycle 3: N=55
Cycle 4: N=21
[56] - SAF
Cycle 1: N=9
Cycle 2: N=36
Cycle 3: N=56

Cycle 4: N=20

[57] - SAF
Cycle 1: N=6
Cycle 2: N=1
Cycle 3: N=4
Cycle 4: N=3

Statistical analyses

No statistical analyses for this end point

Secondary: 16_Number of subjects with serious adverse events by Hysterectomy Status (Hysterectomized and Non-Hysterectomized) -- Efficacy Study Part

End point title	16_Number of subjects with serious adverse events by Hysterectomy Status (Hysterectomized and Non-Hysterectomized) -- Efficacy Study Part

End point description:

Efficacy Study Part
Number of subjects with serious treatment emergent adverse events belonging to the system organ class (SOC) Reproductive system and breast disorders by hysterectomy status (hysterectomized and non-hysterectomized).

End point type	Secondary

End point timeframe:

From Day 1 (first IMP intake) until Week 13 (hysterectomized subjects) or Week 15/16 (non-hysterectomized subjects).

End point values	E4 15 mg Hysterectomized	E4 15 mg Non-Hysterectomized	E4 20 mg Hysterectomized	E4 20 mg Non-Hysterectomized
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	110[58]	103[59]	110[60]	103[61]
Units: N subjects with SAE				
Reproductive System and Breast Disorders	0	5	0	8
Endometrial disorder	0	3	0	4
Endometrial hyperplasia	0	2	0	3
Endometrial metaplasia	0	0	0	1
Hydrosalpinx	0	0	0	0
Uterine polyp	0	0	0	1
Vaginal haemorrhage	0	0	0	1

Notes:

[58] - SAF

[59] - SAF
For non-hysterectomized, all SAEs of SOC Reproductive system and breast disorders were related.

[60] - SAF

[61] - SAF
For non-hysterectomized, all SAEs of SOC Reproductive system and breast disorders were related.

End point values	Placebo Hysterectomized	Placebo Non-Hysterectomized		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110[62]	104[63]		
Units: N subjects with SAE				

Reproductive System and Breast Disorders	0	1		
Endometrial disorder	0	0		
Endometrial hyperplasia	0	0		
Endometrial metaplasia	0	0		
Hydrosalpinx	0	1		
Uterine polyp	0	0		
Vaginal haemorrhage	0	0		

Notes:

[62] - SAF

[63] - SAF
For non-hysterectomized, all SAEs of SOC Reproductive system and breast disorders were related.

Statistical analyses

No statistical analyses for this end point

Secondary: 17_Number of non-hysterectomized subjects with non-serious adverse events -- Efficacy Study Part

End point title	17_Number of non-hysterectomized subjects with non-serious adverse events -- Efficacy Study Part

End point description:

Efficacy Study Part
Number of non-hysterectomized subjects with non-serious treatment emergent adverse events belonging to the system organ class (SOC) Reproductive system and breast disorders.
Frequency threshold for reporting non-serious adverse events: 2%.

End point type	Secondary

End point timeframe:

From Day 1 (first IMP intake) until Week 15/16.

End point values	E4 15 mg Non-Hysterectomized	E4 20 mg Non-Hysterectomized	Placebo Non-Hysterectomized	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	103[64]	103[65]	104[66]	
Units: N subjects with non-serious AEs				
Reproductive System and Breast Disorders	78	84	24	
Vaginal haemorrhage	54	62	14	
Endometrial disorder	43	38	4	
Endometrial thickening	10	13	0	
Breast pain	8	9	2	
Breast tenderness	6	4	0	
Vaginal discharge	6	5	1	
Pelvic pain	1	7	0	
Uterine haemorrhage	3	2	0	
Breast discomfort	1	3	2	
Nipple pain	3	3	0	

Notes:

[64] - SAF

[65] - SAF
[66] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: 18_Number of hysterectomized subjects with non-serious adverse events -- Efficacy Study Part

End point title	18_Number of hysterectomized subjects with non-serious adverse events -- Efficacy Study Part

End point description:

Efficacy Study Part
Number of hysterectomized subjects with non-serious treatment emergent adverse events belonging to the system organ class (SOC) Reproductive system and breast disorders.
Frequency threshold for reporting non-serious adverse events: 2%.

End point type	Secondary

End point timeframe:

From Day 1 (first IMP intake) until Week 13.

End point values	E4 15 mg Hysterectomized	E4 20 mg Hysterectomized	Placebo Hysterectomized	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	110[67]	110[68]	110[69]	
Units: N subjects with non-serious AEs				
Reproductive System and Breast Disorders	20	28	4	
Breast pain	10	14	0	
Nipple pain	3	6	1	
Breast tenderness	3	8	0	
Breast discomfort	1	4	0	
Vaginal discharge	3	1	0	
Vulvovaginal pruritus	3	1	0	

Notes:
[67] - SAF
[68] - SAF
[69] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (first IMP intake) until:
Week 13 for Efficacy Study Part: Hysterectomized participants
Week 15/16 for Efficacy Study Part: Non Hysterectomized participants
Week 55/56 for Safety Study Part: All participants

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs): AEs occurring from time of first IMP intake until last visit or any event already present that worsens (either intensity or frequency) after exposure to the treatment.

MedDRA dictionary: version 24.1 for groups E4 15 mg, E4 20 mg, Placebo; version 25.0. for group E4 20 mg + P4 100 mg.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	ESP - E4 15 mg
Reporting group description: -	
Reporting group title	ESP - E4 20 mg
Reporting group description: -	
Reporting group title	ESP - Placebo
Reporting group description: -	
Reporting group title	SSP - E4 20 mg + P4 100 mg
Reporting group description: -	

Serious adverse events	ESP - E4 15 mg	ESP - E4 20 mg	ESP - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 213 (2.82%)	13 / 213 (6.10%)	1 / 214 (0.47%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Concussion			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine perforation			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superficial vein thrombosis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Migraine			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transverse sinus thrombosis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential tremor			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial disorder			
subjects affected / exposed	3 / 213 (1.41%)	4 / 213 (1.88%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	3 / 3	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			

subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectocele			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	2 / 213 (0.94%)	3 / 213 (1.41%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial metaplasia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrosalpinx			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	1 / 214 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			

subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 213 (0.00%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 213 (0.47%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypocalcaemia			

subjects affected / exposed	0 / 213 (0.00%)	1 / 213 (0.47%)	0 / 214 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SSP - E4 20 mg + P4 100 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 922 (3.47%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	2 / 922 (0.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			

subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine perforation				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Superficial vein thrombosis				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transverse sinus thrombosis				
subjects affected / exposed	1 / 922 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Essential tremor				

subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometrial disorder			
subjects affected / exposed	7 / 922 (0.76%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	5 / 922 (0.54%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Rectocele			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine haemorrhage			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial hyperplasia			

subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial metaplasia			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydrosalpinx			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine polyp			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal polyp			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 922 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 922 (0.43%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 922 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	ESP - E4 15 mg	ESP - E4 20 mg	ESP - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	116 / 213 (54.46%)	123 / 213 (57.75%)	44 / 214 (20.56%)
Investigations			
Weight increased			
subjects affected / exposed	6 / 213 (2.82%)	1 / 213 (0.47%)	1 / 214 (0.47%)
occurrences (all)	6	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Uterine leiomyoma			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	0 / 214 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 213 (2.35%)	2 / 213 (0.94%)	2 / 214 (0.93%)
occurrences (all)	5	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 213 (11.74%)	18 / 213 (8.45%)	24 / 214 (11.21%)
occurrences (all)	39	22	49
Dizziness			
subjects affected / exposed	3 / 213 (1.41%)	7 / 213 (3.29%)	2 / 214 (0.93%)
occurrences (all)	3	7	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 213 (1.88%)	6 / 213 (2.82%)	0 / 214 (0.00%)
occurrences (all)	4	6	0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	55 / 213 (25.82%)	63 / 213 (29.58%)	14 / 214 (6.54%)
occurrences (all)	110	155	22
Endometrial disorder			
subjects affected / exposed	43 / 213 (20.19%)	38 / 213 (17.84%)	4 / 214 (1.87%)
occurrences (all)	43	38	4
Breast pain			
subjects affected / exposed	18 / 213 (8.45%)	23 / 213 (10.80%)	2 / 214 (0.93%)
occurrences (all)	20	23	2
Breast tenderness			
subjects affected / exposed	9 / 213 (4.23%)	12 / 213 (5.63%)	0 / 214 (0.00%)
occurrences (all)	9	15	0
Endometrial thickening			
subjects affected / exposed	10 / 213 (4.69%)	13 / 213 (6.10%)	0 / 214 (0.00%)
occurrences (all)	10	13	0
Nipple pain			

subjects affected / exposed	6 / 213 (2.82%)	9 / 213 (4.23%)	1 / 214 (0.47%)
occurrences (all)	6	11	2
Vaginal discharge			
subjects affected / exposed	9 / 213 (4.23%)	6 / 213 (2.82%)	1 / 214 (0.47%)
occurrences (all)	9	7	1
Breast discomfort			
subjects affected / exposed	2 / 213 (0.94%)	7 / 213 (3.29%)	2 / 214 (0.93%)
occurrences (all)	2	7	2
Pelvic pain			
subjects affected / exposed	1 / 213 (0.47%)	7 / 213 (3.29%)	2 / 214 (0.93%)
occurrences (all)	1	9	2
Vulvovaginal pruritus			
subjects affected / exposed	5 / 213 (2.35%)	3 / 213 (1.41%)	1 / 214 (0.47%)
occurrences (all)	5	3	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 213 (2.35%)	9 / 213 (4.23%)	3 / 214 (1.40%)
occurrences (all)	8	9	3
Abdominal pain			
subjects affected / exposed	5 / 213 (2.35%)	6 / 213 (2.82%)	7 / 214 (3.27%)
occurrences (all)	5	6	7
Abdominal pain lower			
subjects affected / exposed	6 / 213 (2.82%)	7 / 213 (3.29%)	2 / 214 (0.93%)
occurrences (all)	6	10	2
Abdominal pain upper			
subjects affected / exposed	2 / 213 (0.94%)	0 / 213 (0.00%)	2 / 214 (0.93%)
occurrences (all)	2	0	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 213 (0.47%)	6 / 213 (2.82%)	5 / 214 (2.34%)
occurrences (all)	1	6	7
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 213 (0.94%)	7 / 213 (3.29%)	4 / 214 (1.87%)
occurrences (all)	2	8	4
Back pain			

subjects affected / exposed	4 / 213 (1.88%)	3 / 213 (1.41%)	2 / 214 (0.93%)
occurrences (all)	4	4	3
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 213 (4.23%)	9 / 213 (4.23%)	6 / 214 (2.80%)
occurrences (all)	9	9	6
Upper respiratory tract infection			
subjects affected / exposed	1 / 213 (0.47%)	0 / 213 (0.00%)	2 / 214 (0.93%)
occurrences (all)	2	0	2

Non-serious adverse events	SSP - E4 20 mg + P4 100 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	775 / 922 (84.06%)		
Investigations			
Weight increased			
subjects affected / exposed	11 / 922 (1.19%)		
occurrences (all)	11		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	28 / 922 (3.04%)		
occurrences (all)	29		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 922 (0.65%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	88 / 922 (9.54%)		
occurrences (all)	133		
Dizziness			
subjects affected / exposed	14 / 922 (1.52%)		
occurrences (all)	14		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 922 (0.87%)		
occurrences (all)	8		
Reproductive system and breast			

disorders			
Vaginal haemorrhage			
subjects affected / exposed	616 / 922 (66.81%)		
occurrences (all)	2382		
Endometrial disorder			
subjects affected / exposed	145 / 922 (15.73%)		
occurrences (all)	147		
Breast pain			
subjects affected / exposed	89 / 922 (9.65%)		
occurrences (all)	95		
Breast tenderness			
subjects affected / exposed	64 / 922 (6.94%)		
occurrences (all)	67		
Endometrial thickening			
subjects affected / exposed	55 / 922 (5.97%)		
occurrences (all)	55		
Nipple pain			
subjects affected / exposed	24 / 922 (2.60%)		
occurrences (all)	25		
Vaginal discharge			
subjects affected / exposed	17 / 922 (1.84%)		
occurrences (all)	21		
Breast discomfort			
subjects affected / exposed	23 / 922 (2.49%)		
occurrences (all)	24		
Pelvic pain			
subjects affected / exposed	10 / 922 (1.08%)		
occurrences (all)	12		
Vulvovaginal pruritus			
subjects affected / exposed	8 / 922 (0.87%)		
occurrences (all)	8		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	18 / 922 (1.95%)		
occurrences (all)	19		
Abdominal pain			

subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	37 / 922 (4.01%) 48 48 / 922 (5.21%) 58 20 / 922 (2.17%) 20		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	11 / 922 (1.19%) 11		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	14 / 922 (1.52%) 16 23 / 922 (2.49%) 27		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	57 / 922 (6.18%) 58 19 / 922 (2.06%) 20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2019	Amendment 1, leading to version 2.0 of the protocol, date November 28, 2019 Inclusion criterion was added for non hysterectomized subjects regarding uterus with bi-layer endometrial thickness ≤ 4 mm on TVUS. Exclusion criterion regarding diabetes mellitus was changed from "fasting glucose outside the normal ranges and glycated hemoglobin above 7%" To "fasting glucose outside the normal ranges and/or glycated hemoglobin above 7%". Exclusion criterion regarding dyslipoproteinemia was changed from "(LDL >190 mg/dL and triglycerides >300 mg/dL)" to "(LDL >190 mg/dL and/or triglycerides >300 mg/dL)". Exclusion criterion regarding smoking was changed from 5 cigarettes per day to 15 cigarettes per day. The number of packs per week has been deleted. Exclusion criterion was changed from "Inadequately treated hyperthyroidism at screening" to "Inadequately treated hyperthyroidism with abnormal TSH and free T4 at screening. Subjects with low TSH are allowed if free T4 at screening is within normal range."
24 February 2020	Amendment 2, leading to version 3.0 of the protocol, date February 24, 2020 Exclusion criterion updated to cover not only "enlarged uterus with myoma" but also "any uterine/endometrial abnormality which in the judgment of the investigator contraindicates the use of estrogen and/or progestin therapy". Exclusion criterion changed for clarification: "Diabetes mellitus with poor glycemic control in the last 6 months assessed by fasting glucose outside the normal ranges and glycated hemoglobin above 7%" was replaced with "Laboratory values of fasting glucose above 125 mg/dL (>6.94 mmol/L) and/or glycated hemoglobin above 7%".
09 July 2020	Amendment 3, leading to version 4.0 of the protocol, date July 09, 2020 Inclusion criterion regarding mammography and BI-RADS 0 was adjusted to clarify that a BI-RADS 0 may be acceptable if further assessment is done confirming non clinical significant changes. Addition of a section about Adverse Events of Special Interest (AESIs) to the protocol.

05 August 2021	Amendment 4.1, leading to version 5.1 of the protocol, date August 05, 2021 Disordered proliferative endometrium (DPE) removed from the reasons for study discontinuation and exclusion criteria, to align with regulatory approach and based on the available safety information. Extended the maximum screening period; increased the planned number of subjects to be enrolled in Arm 4 based on the available safety information; added information regarding COVID-19 vaccination during the trial, including a recommendation on the timing of vaccination in relation to study assessments. Updated the definition for the hierarchy of the pathologic diagnoses of endometrial tissue. Defined the process for resolution of endometrial events. Increased the number of pathologists who assessed endometrial biopsies and clarified pathologists' roles. Clarified secondary efficacy endpoints regarding frequency and severity of vasomotor symptoms (VMS); added information regarding restart patients on study treatment after study drug interruption. Specified that exclusion criterion about high risk oncogene human papilloma virus (HPV) included subtypes 16 and 18. Endometrial and General Safety Study part: Safety endpoints for endometrial safety were adjusted. Added information text that P4 200 mg may be administered after treatment discontinuation due to vaginal bleeding or endometrial event if deemed necessary by the Investigator.
27 April 2022	Amendment 5, leading to version 6.0 of the protocol, date April 27, 2022 Following interaction with FDA regarding the study, disordered proliferative endometrium was reincluded as an exclusion criterion and as a reason for discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.

Notes: