Clinical trial results:
A Multicentre Dose-Finding, Randomised, Double-Blind, Placebo-Controlled Study to Select the Daily Oral Dose of Estetrol (E4) for the Treatment of Vasomotor Symptoms in Post-Menopausal Women

Summary

EudraCT number	2015-004018-44
Trial protocol	BE NL PL GB CZ IE
Global end of trial date	22 January 2018

Results information

Result version number	v1 (current)
This version publication date	07 November 2019
First version publication date	07 November 2019

Trial information

Trial identification

Sponsor protocol code	MIT-Do0001-C201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02834312
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mithra Pharmaceuticals SA
Sponsor organisation address	Rue Saint-Georges 5-7, Liege, Belgium, 4000
Public contact	Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals SA, +32 43492822, clinicaltrials@mithra.com
Scientific contact	Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals SA, +32 43492822, clinicaltrials@mithra.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2018
Global end of trial reached?	Yes
Global end of trial date	22 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To define the minimum effective dose (MED) of the oral dose of estetrol (E4) by evaluating changes in frequency and in severity of moderate to severe vasomotor symptoms (VMS).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki, Good Clinical Practice (GCP) as defined in the International Council for Harmonisation (ICH), and all applicable national laws and regulations including but not limited to country-specific GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Czech Republic: 45
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Poland: 168
Worldwide total number of subjects	260
EEA total number of subjects	260

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)	260

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 609 participants were screened, with 349 resulting in screen failures. A total of 260 participants were enrolled across 35 sites in 5 European countries, with 257 participants receiving at least one dose of study drug. Each participant was randomly allocated to one of 5 treatment groups in a 1:1:1:1:1 ratio.

Period 1

Period 1 title	Overall Study (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

Arms

Are arms mutually exclusive?	Yes
Arm title	E4 2.5 mg

Arm description:

Estetrol (E4) 2.5 mg was administered orally via a capsule, once daily.

Arm type	Experimental
Investigational medicinal product name	Estetrol
Investigational medicinal product code	E4
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 2.5, 5, 10 or 15 mg of estetrol (E4) capsule orally, once daily for 12 consecutive weeks.

Arm title	E4 5 mg

Arm description:

Estetrol (E4) 5 mg was administered orally via a capsule, once daily.

Arm type	Experimental
Investigational medicinal product name	Estetrol
Investigational medicinal product code	E4
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 2.5, 5, 10 or 15 mg of estetrol (E4) capsule orally, once daily for 12 consecutive weeks.

Arm title	E4 10 mg

Arm description:

Estetrol (E4) 10 mg was administered orally via a capsule, once daily.

Arm type	Experimental

Investigational medicinal product name	Estetrol
Investigational medicinal product code	E4
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 2.5, 5, 10 or 15 mg of estetrol (E4) capsule orally, once daily for 12 consecutive weeks.

Arm title	E4 15 mg

Arm description:

Estetrol (E4) 15 mg was administered orally via a capsule, once daily.

Arm type	Experimental
Investigational medicinal product name	Estetrol
Investigational medicinal product code	E4
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 2.5, 5, 10 or 15 mg of estetrol (E4) capsule orally, once daily for 12 consecutive weeks.

Arm title	Placebo

Arm description:

Matching placebo was administered orally via a capsule, once daily.

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

Dosage and administration details:

Matching placebo capsule, administered orally once daily for 12 consecutive weeks.

Number of subjects in period 1[1]	E4 2.5 mg	E4 5 mg	E4 10 mg
Started	52	47	54
Completed	43	36	39
Not completed	9	11	15
Consent withdrawn by subject	4	4	6
Adverse event, non-fatal	-	2	3
Deterioration of clinical condition	-	-	1
Miscellaneous	1	1	3
Protocol deviation	4	4	2

Number of subjects in period 1[1]	E4 15 mg	Placebo
Started	49	55

Completed	41	41
Not completed	8	14
Consent withdrawn by subject	3	7
Adverse event, non-fatal	1	1
Deterioration of clinical condition	-	-
Miscellaneous	2	3
Protocol deviation	2	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 260 participants were randomized to treatment groups, but 3 participants did not receive study drug. Only participants who received study drug are included in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	E4 2.5 mg
Reporting group description:	
Estetrol (E4) 2.5 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 5 mg
Reporting group description:	
Estetrol (E4) 5 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 10 mg
Reporting group description:	
Estetrol (E4) 10 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 15 mg
Reporting group description:	
Estetrol (E4) 15 mg was administered orally via a capsule, once daily.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered orally via a capsule, once daily.	

Reporting group values	E4 2.5 mg	E4 5 mg	E4 10 mg
Number of subjects	52	47	54
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	52	47	54
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.0	53.8	54.3
standard deviation	± 4.42	± 4.75	± 4.44
Gender categorical Units: Subjects			
Female	52	47	54
Male	0	0	0
Race Units: Subjects			
White	52	47	54
Smoker Units: Subjects			
No	46	43	43
Yes	6	4	11

Reporting group values	E4 15 mg	Placebo	Total
Number of subjects	49	55	257
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	49	55	257
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.2	53.7	
standard deviation	± 4.03	± 4.41	-
Gender categorical Units: Subjects			
Female	49	55	257
Male	0	0	0
Race Units: Subjects			
White	49	55	257
Smoker Units: Subjects			
No	47	47	226
Yes	2	8	31

End points

End points reporting groups

Reporting group title	E4 2.5 mg
Reporting group description:	
Estetrol (E4) 2.5 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 5 mg
Reporting group description:	
Estetrol (E4) 5 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 10 mg
Reporting group description:	
Estetrol (E4) 10 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 15 mg
Reporting group description:	
Estetrol (E4) 15 mg was administered orally via a capsule, once daily.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered orally via a capsule, once daily.	

Primary: Change in Weekly Frequency of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 4

End point title	Change in Weekly Frequency of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 4

End point description:

The severity scoring system of VMS was documented by the participants in the participant's diary using the following scores:
None (0) = no VMS symptoms
Mild (1) = Sensation of heat without sweating
Moderate (2) = Sensation of heat with sweating. Able to continue activity
Severe (3) = Sensation of heat with sweating. Causes cessation of activity

The weekly frequency of moderate to severe VMS at baseline and week 4 is defined as the total number of all recorded moderate to severe VMS experienced during the 7 day periods days -7 to -1 (baseline) and days 22 to 28 (week 4), respectively. Change = total No. of moderate & severe VMS at week 4 - total No. of moderate & severe VMS at baseline. A negative change from baseline score indicates a reduction in the frequency of moderate to severe VMS per week.

Reported value are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Primary

End point timeframe:

Baseline and Week 4

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[1]	47[2]	53[3]	49[4]
Units: Weekly Frequency				
arithmetic mean (standard deviation)	-35.9 (± 31.57)	-27.6 (± 22.47)	-36.4 (± 22.62)	-41.4 (± 21.60)

Notes:

[1] - ITT N = 53
ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach
[2] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

[3] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

[4] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[5]			
Units: Weekly Frequency				
arithmetic mean (standard deviation)	-32.9 (± 23.14)			

Notes:

[5] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9986
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.16
upper limit	12.11

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5389
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	5.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.58
upper limit	17.14

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9673
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.24
upper limit	8.8

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0683
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-10.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.98
upper limit	0.57

Primary: Change in Weekly Frequency of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 12

End point title	Change in Weekly Frequency of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 12

End point description:

The severity scoring system of VMS was documented by the participants in the participants diary using the following scores:
None (0) = no VMS symptoms
Mild (1) = Sensation of heat without sweating

Moderate (2) = Sensation of heat with sweating. Able to continue activity
Severe (3) = Sensation of heat with sweating. Causes cessation of activity

The weekly frequency of moderate to severe VMS at baseline and week 12 is defined as the total number of all recorded moderate to severe VMS experienced during the 7 day periods days -7 to -1 (baseline) and days 78 to 84 (week 12) respectively. Change = total No. of moderate & severe VMS at week 12 - total No. of moderate & severe VMS at baseline. A negative change from baseline score indicates a reduction in the frequency of moderate to severe VMS per week.

Reported value are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[6]	47[7]	53[8]	49[9]
Units: Weekly frequency				
arithmetic mean (standard deviation)	-45.0 (± 38.91)	-40.6 (± 24.37)	-47.2 (± 22.87)	-50.9 (± 18.38)

Notes:

[6] - ITT N = 53
ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach
[7] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

[8] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

[9] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[10]			
Units: Weekly frequency				
arithmetic mean (standard deviation)	-43.0 (± 22.31)			

Notes:

[10] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8986
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	3.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.24
upper limit	14.73

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9326
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	2.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	14.63

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9491
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.97
upper limit	8.76

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0706
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-10.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.6
upper limit	0.65

Primary: Change in Mean Severity of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 4

End point title	Change in Mean Severity of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 4

End point description:

The severity scoring system of VMS was documented by the participants in the participants diary using the following scores:
None (0) = no VMS symptoms
Mild (1) = Sensation of heat without sweating
Moderate (2) = Sensation of heat with sweating. Able to continue activity
Severe (3) = Sensation of heat with sweating. Causes cessation of activity

Change in the severity of VMS from baseline to week 4 is defined as arithmetic mean of the recorded severity score of VMS (mild, moderate and severe) observed during day 22 & 28 (week 4) - the arithmetic mean of recorded severity scores values of VMS (moderate or severe) observed during -7 to -1 prior to treatment (baseline). A negative change from baseline score indicates improvement in symptoms.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Primary

End point timeframe:

Baseline and Week 4

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[11]	47[12]	53[13]	49[14]
Units: Score on a Scale				
arithmetic mean (standard deviation)	-0.3 (± 0.55)	-0.2 (± 0.46)	-0.5 (± 0.60)	-0.6 (± 0.64)

Notes:

[11] - ITT N = 53
ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach
[12] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

[13] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

[14] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	55[15]			
Units: Score on a Scale				
arithmetic mean (standard deviation)	-0.3 (± 0.41)			

Notes:

[15] - ITT set with baseline and week 4 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9998
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.24

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8253
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.35

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3767
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.1

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0486
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0

Primary: Change in Mean Severity of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 12

End point title	Change in Mean Severity of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 12

End point description:

The severity scoring system of VMS was documented by the participants in the participants diary using the following scores:
None (0) = no VMS symptoms
Mild (1) = Sensation of heat without sweating
Moderate (2) = Sensation of heat with sweating. Able to continue activity
Severe (3) = Sensation of heat with sweating. Causes cessation of activity

Change in the severity of VMS from baseline to week 12 is defined as arithmetic mean of the recorded severity score of VMS (mild, moderate and severe) observed during day 78 to 84 (week 12) - the arithmetic mean of recorded severity scores values of VMS (moderate or severe) observed during -7 to -1 prior to treatment (baseline). A negative change from baseline score indicates improvement in symptoms.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[16]	47[17]	53[18]	49[19]
Units: Score on a Scale				
arithmetic mean (standard deviation)	-0.6 (± 0.79)	-0.4 (± 0.67)	-0.7 (± 0.80)	-1.0 (± 0.87)

Notes:

[16] - ITT N = 53
ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

[17] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

[18] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

[19] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[20]			
Units: Score on a Scale				
arithmetic mean (standard deviation)	-0.7 (± 0.78)			

Notes:

[20] - ITT set with baseline and week 12 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9992
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.4

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3062
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.64

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9981
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.34

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0489
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0

Secondary: Change in Genitourinary Syndrome of Menopause (GSM) from Baseline

to Week 13

End point title	Change in Genitourinary Syndrome of Menopause (GSM) from Baseline to Week 13

End point description:

The following GSM symptoms were assessed:
Vaginal dryness
Vaginal and/or irritation/itching
Dysuria
Vaginal pain associated with sexual activity
These GSM symptoms were graded by the participants using the following scale: [0] none, [1] mild, [2] moderate, or [3] severe. A negative change from baseline score indicates improvement in symptoms.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[21]	47[22]	53[23]	48[24]
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Vaginal dryness	-0.4 (± 0.82)	-0.7 (± 0.98)	-0.5 (± 0.80)	-0.6 (± 0.98)
Vaginal and/or vulvar irritation/itching	-0.5 (± 0.80)	-0.2 (± 1.00)	-0.4 (± 0.88)	-0.1 (± 0.86)
Dysuria	-0.2 (± 0.57)	-0.1 (± 0.58)	-0.2 (± 0.58)	-0.0 (± 0.64)
Vaginal pain associated with sexual activity	-0.2 (± 0.62)	-0.6 (± 1.02)	-0.4 (± 0.75)	-0.4 (± 0.77)

Notes:

[21] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[22] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[23] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[24] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[25]			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Vaginal dryness	-0.4 (± 1.01)			
Vaginal and/or vulvar irritation/itching	-0.3 (± 0.91)			
Dysuria	-0.1 (± 0.66)			
Vaginal pain associated with sexual activity	-0.2 (± 0.91)			

Notes:

[25] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	Vaginal Dryness: E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3345
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.13

Statistical analysis title	Vaginal Dryness: E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1202
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.05

Statistical analysis title	Vaginal Dryness: E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0798
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.03

Statistical analysis title	Vaginal Dryness: E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0291
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.03

Statistical analysis title	Irritation/Itching: E4 2.5 mg vs Placebo
Statistical analysis description: Vaginal and/or vulvar irritation/itching	
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1717
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.06

Statistical analysis title	Irritation/Itching: E4 5 mg vs Placebo
Statistical analysis description: Vaginal and/or vulvar irritation/itching	
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9618
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.24

Statistical analysis title	Irritation/Itching: E4 10 mg vs Placebo
Statistical analysis description: Vaginal and/or vulvar irritation/itching	
Comparison groups	Placebo v E4 10 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2487
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.09

Statistical analysis title	Irritation/Itching: E4 15 mg vs Placebo
Statistical analysis description: Vaginal and/or vulvar irritation/itching	
Comparison groups	Placebo v E4 15 mg
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.931
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.23

Statistical analysis title	Dysuria: E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2942
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.06

Statistical analysis title	Dysuria: E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3488
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.07

Statistical analysis title	Dysuria: E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3386
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.07

Statistical analysis title	Dysuria: E4 15 mg vs Placebo

Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.643
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.27

Statistical analysis title	Vaginal Pain: E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0763
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.02

Statistical analysis title	Vaginal Pain: E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0246
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.03

Statistical analysis title	Vaginal Pain: E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0004
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.18

Statistical analysis title	Vaginal Pain: E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0006
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.17

Secondary: Change in Vaginal Bleeding Associated with Sexual Activity from Baseline to Week 13

End point title	Change in Vaginal Bleeding Associated with Sexual Activity from Baseline to Week 13

End point description:

Vaginal bleeding (a genitourinary syndrome of menopasure [GSM]) associated with sexual activity was documented using 3 categories: [0] absent, [1] present, or not applicable.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[26]	47[27]	53[28]	49[29]
Units: Participants				
Baseline: Presence	0	3	0	0
Baseline: Absence	53	43	53	47
Baseline: Not Applicable	0	1	0	1
Week 13: Presence	0	0	0	2
Week 13: Absence	53	47	53	46
Week 13: Not Applicable	0	0	0	0

Notes:

[26] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[27] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[28] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[29] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[30]			
Units: Participants				
Baseline: Presence	2			
Baseline: Absence	51			
Baseline: Not Applicable	2			
Week 13: Presence	2			
Week 13: Absence	53			
Week 13: Not Applicable	0			

Notes:

[30] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	Vaginal Bleeding: 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9958
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-459.49
upper limit	457.01

Statistical analysis title	Vaginal Bleeding: 5 mg vs Placebo
Comparison groups	Placebo v E4 5 mg

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.903
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-30.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-529.01
upper limit	467.05

Statistical analysis title	Vaginal Bleeding: 10 mg vs Placebo
Comparison groups	Placebo v E4 10 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9955
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-461.01
upper limit	458.34

Statistical analysis title	Vaginal Bleeding: 15 mg vs Placebo
Comparison groups	Placebo v E4 15 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9308
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	10.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-223.76
upper limit	244.51

Secondary: Change in Menopause Rating Scale (MRS) Score from Baseline to Week 5

End point title	Change in Menopause Rating Scale (MRS) Score from Baseline to Week 5

End point description:

MRS consists of 11 items (severity expressed in 0 to 4 points in each item). The total score of the MRS ranges between 0 (asymptomatic) to 44 (highest degree of complaints).
A negative change from baseline indicates an improvement in symptoms.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 5

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[31]	47[32]	53[33]	48[34]
Units: Score on a Scale				
arithmetic mean (standard deviation)	-6.2 (± 5.67)	-6.0 (± 6.21)	-6.0 (± 6.44)	-7.8 (± 7.56)

Notes:

[31] - ITT N = 53
ITT set with baseline and week 5 data, last observation carried forward [LOCF] approach
[32] - ITT set with baseline and week 5 data, last observation carried forward [LOCF] approach

[33] - ITT set with baseline and week 5 data, last observation carried forward [LOCF] approach

[34] - ITT set with baseline and week 5 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[35]			
Units: Score on a Scale				
arithmetic mean (standard deviation)	-5.4 (± 6.46)			

Notes:

[35] - ITT set with baseline and week 5 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4352
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	1.09

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4808
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.02
upper limit	1.19

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8994
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	1.81

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0113
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-3.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	-0.56

Secondary: Change in Menopause Rating Scale (MRS) Score from Baseline to Week 13

End point title	Change in Menopause Rating Scale (MRS) Score from Baseline to Week 13

End point description:

MRS consists of 11 items (severity expressed in 0 to 4 points in each item). The total score of the MRS ranges between 0 (asymptomatic) to 44 (highest degree of complaints).
A negative change from baseline indicates an improvement in symptoms.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[36]	47[37]	53[38]	48[39]
Units: Score on a Scale				
arithmetic mean (standard deviation)	-7.0 (± 6.29)	-5.5 (± 7.23)	-7.9 (± 8.30)	-8.3 (± 7.90)

Notes:

[36] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[37] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[38] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[39] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[40]			
Units: Score on a Scale				
arithmetic mean (standard deviation)	-6.8 (± 8.67)			

Notes:

[40] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	Placebo v E4 2.5 mg

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5283
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.74
upper limit	1.52

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9965
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	2.81

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4726
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.77
upper limit	1.39

Statistical analysis title	E4 15 mg vs Placebo

Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0694
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.32
upper limit	0.17

Secondary: Change in Vaginal pH from Baseline to Week 13

End point title	Change in Vaginal pH from Baseline to Week 13

End point description:

Vaginal pH was performed on-site by an investigator or qualified site personnel using a standardized vaginal pH paper test.

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[41]	47[42]	53[43]	49[44]
Units: pH				
arithmetic mean (standard deviation)	-0.16 (± 0.746)	-0.22 (± 1.173)	-0.08 (± 0.780)	-0.12 (± 0.550)

Notes:

[41] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[42] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[43] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[44] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[45]			
Units: pH				
arithmetic mean (standard deviation)	0.12 (± 0.719)			

Notes:

[45] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2294
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.08

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9948
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.27

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9818
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.25

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3352
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.11

Secondary: Change in Vaginal Maturation Value (MV) from Baseline to Week 13

End point title	Change in Vaginal Maturation Value (MV) from Baseline to Week 13

End point description:

A vaginal MV is a parameter derived from the maturation index (MI). The MI is a ratio obtained through performing a random count of three major cell types (parabasal cells, intermediate cells and superficial cells) that are shed from squamous epithelium. The cell count is expressed as a percentage that reads as follows:
MI = % parabasal cells, % intermediate cells, % superficial cells.
The vaginal MV is calculated as follows:
MV = 0.0 x parabasal cells [%] + 0.5 x intermediate cells [%] + 1.0 x superficial cells [%]

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[46]	44[47]	52[48]	47[49]
Units: Maturation value				
arithmetic mean (standard deviation)	16.1 (± 24.63)	26.6 (± 29.31)	26.5 (± 27.89)	30.1 (± 28.98)

Notes:

[46] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[47] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[48] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[49] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[50]			
Units: Maturation value				
arithmetic mean (standard deviation)	6.7 (± 16.21)			

Notes:

[50] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0003
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	14.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.71
upper limit	23.48

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	Placebo v E4 5 mg
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	19.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.93
upper limit	28.38

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	23.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.72
upper limit	32.49

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	22.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.43
upper limit	31.59

Secondary: Change in Serum Concentration of Triglycerides from Baseline to Week 13

End point title	Change in Serum Concentration of Triglycerides from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[51]	47[52]	53[53]	49[54]
Units: mmol/L				
arithmetic mean (standard deviation)	-0.0392 (± 0.48013)	-0.0146 (± 0.79080)	0.0320 (± 0.90955)	0.2018 (± 0.80108)

Notes:

[51] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[52] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[53] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[54] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[55]			
Units: mmol/L				
arithmetic mean (standard deviation)	0.0070 (± 0.77504)			

Notes:

[55] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4821
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.14

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8945
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.22

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 1
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.3

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6721
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.44

Secondary: Change in Serum Concentration of High Density Lipoprotein (HDL) Cholesterol from Baseline to Week 13

End point title	Change in Serum Concentration of High Density Lipoprotein (HDL) Cholesterol from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:
Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[56]	47[57]	53[58]	49[59]
Units: mmol/L				
arithmetic mean (standard deviation)	0.1169 (± 0.20512)	0.1113 (± 0.28608)	0.1496 (± 0.24857)	0.1596 (± 0.23372)

Notes:
[56] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[57] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[58] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[59] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[60]			
Units: mmol/L				
arithmetic mean (standard deviation)	0.0146 (± 0.21852)			

Notes:
[60] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	Placebo v E4 2.5 mg
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0481
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.22

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	Placebo v E4 5 mg

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0451
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.22

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0076
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.24

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0025
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.26

Secondary: Change in Serum Concentration of Low Density Lipoprotein (LDL)

Cholesterol from Baseline to Week 13

End point title	Change in Serum Concentration of Low Density Lipoprotein (LDL) Cholesterol from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[61]	47[62]	53[63]	49[64]
Units: mmol/L				
arithmetic mean (standard deviation)	0.2263 (± 0.58921)	0.2805 (± 0.66790)	0.1763 (± 0.75712)	0.0835 (± 0.43864)

Notes:

[61] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[62] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[63] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[64] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[65]			
Units: mmol/L				
arithmetic mean (standard deviation)	0.0989 (± 0.55484)			

Notes:

[65] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8037
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.38

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4627
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.44

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.952
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.34

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9308
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.21

Secondary: Change in Total Cholesterol from Baseline to Week 13

End point title	Change in Total Cholesterol from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[66]	47[67]	53[68]	49[69]
Units: mmol/L				
arithmetic mean (standard deviation)	0.2175 (± 0.64351)	0.2165 (± 0.83013)	0.2614 (± 0.85508)	0.1285 (± 0.71395)

Notes:

[66] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[67] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[68] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[69] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[70]			
Units: mmol/L				
arithmetic mean (standard deviation)	0.0010 (± 0.70271)			

Notes:

[70] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5863
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.5

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5027
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.53

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3051
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.55

Statistical analysis title	E4 15 mg vs Placebo

Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9873
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.39

Secondary: Change in Fasting Glucose from Baseline to Week 13

End point title	Change in Fasting Glucose from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[71]	46[72]	52[73]	49[74]
Units: mmol/L				
arithmetic mean (standard deviation)	-0.013 (± 0.3704)	-0.038 (± 0.6564)	-0.157 (± 0.5321)	0.019 (± 0.5131)

Notes:

[71] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[72] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[73] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[74] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	53[75]			
Units: mmol/L				
arithmetic mean (standard deviation)	0.006 (± 0.4195)			

Notes:

[75] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.983
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.27

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9983
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.21

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7535
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.14

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 1
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.24

Secondary: Change in Insulin Levels from Baseline to Week 13

End point title	Change in Insulin Levels from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[76]	47[77]	53[78]	49[79]
Units: mIU/L				
arithmetic mean (standard deviation)	-0.86 (± 11.667)	-0.83 (± 21.145)	-1.82 (± 9.382)	-1.40 (± 7.146)

Notes:

[76] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[77] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[78] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[79] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[80]			
Units: mIU/L				
arithmetic mean (standard deviation)	2.55 (± 8.912)			

Notes:
[80] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5945
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.61
upper limit	2.7

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4737
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.19
upper limit	2.4

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.325
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-3.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.47
upper limit	1.83

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1255
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-4.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.67
upper limit	0.82

Secondary: Change in Serum Concentration of Glycated Hemoglobin from Baseline to Week 13

End point title	Change in Serum Concentration of Glycated Hemoglobin from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[81]	47[82]	53[83]	49[84]
Units: mmol/mol				
arithmetic mean (standard deviation)	0.02 (± 0.222)	0.00 (± 0.190)	-0.08 (± 0.175)	-0.14 (± 0.225)

Notes:

[81] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[82] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[83] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[84] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[85]			
Units: mmol/mol				
arithmetic mean (standard deviation)	0.02 (± 0.194)			

Notes:

[85] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9988
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	0.94

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9768
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	0.87

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0272
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	-0.1

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0001
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.83
upper limit	-0.74

Secondary: Change in Homeostatis Model Assessment-Estimated Insulin Resistance (HOMA-IR) from Baseline to Week 13

End point title	Change in Homeostatis Model Assessment-Estimated Insulin Resistance (HOMA-IR) from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:
Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[86]	45[87]	53[88]	49[89]
Units: Index				
arithmetic mean (standard deviation)	-0.08 (± 2.585)	-0.52 (± 6.815)	-0.42 (± 2.204)	-0.36 (± 1.845)

Notes:

[86] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[87] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[88] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[89] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[90]			
Units: Index				
arithmetic mean (standard deviation)	0.58 (± 2.179)			

Notes:

[90] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8842
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	0.99

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4794
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	0.67

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6434
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	0.78

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2155
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	0.38

Secondary: Change in Serum Concentration of Prothrombin Fragment 1 + 2 from

Baseline to Week 13

End point title	Change in Serum Concentration of Prothrombin Fragment 1 + 2 from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[91]	46[92]	53[93]	49[94]
Units: pmol/L				
arithmetic mean (standard deviation)	4.53 (± 201.865)	43.30 (± 333.608)	17.44 (± 287.119)	30.07 (± 309.723)

Notes:

[91] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[92] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[93] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[94] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[95]			
Units: pmol/L				
arithmetic mean (standard deviation)	-33.20 (± 395.547)			

Notes:

[95] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8345
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-39.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-160.16
upper limit	80.28

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9997
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-7.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-128.17
upper limit	113.95

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9197
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-86.92
upper limit	148.72

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9515
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	27.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-94.61
upper limit	149.64

Secondary: Change in Serum Concentration of D-dimers from Baseline to Week 13

End point title	Change in Serum Concentration of D-dimers from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[96]	46[97]	53[98]	49[99]
Units: mcg/L				
arithmetic mean (standard deviation)	5.8 (± 158.93)	80.4 (± 327.02)	50.9 (± 139.54)	108.2 (± 293.57)

Notes:

[96] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[97] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[98] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[99] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[100]			
Units: mcg/L				
arithmetic mean (standard deviation)	127.8 (± 542.68)			

Notes:

[100] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1827
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-122.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-282.11
upper limit	36.59

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8116
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-56.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-220.78
upper limit	106.93

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	Placebo v E4 10 mg
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.579
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-76.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-235.08
upper limit	81.57

Statistical analysis title	E4 15 mg vs Placebo

Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.998
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-15.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-176.73
upper limit	146.04

Secondary: Change in Serum Concentration of Sex-Hormone Binding Globulin from Baseline to Week 13

End point title	Change in Serum Concentration of Sex-Hormone Binding Globulin from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[101]	46[102]	53[103]	49[104]
Units: nmol/L				
arithmetic mean (standard deviation)	4.26 (± 15.874)	11.33 (± 14.233)	28.97 (± 26.846)	40.63 (± 32.658)

Notes:

[101] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[102] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[103] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[104] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[105]			
Units: nmol/L				
arithmetic mean (standard deviation)	1.98 (± 13.080)			

Notes:

[105] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.973
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.61
upper limit	12.65

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1092
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	9.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	20.05

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	26.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.34
upper limit	37.1

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	38.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.87
upper limit	48.95

Secondary: Change in Serum Concentration of Antithrombin from Baseline to Week 13

End point title	Change in Serum Concentration of Antithrombin from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[106]	46[107]	53[108]	49[109]
Units: percent				
arithmetic mean (standard deviation)	-3.7 (± 16.02)	-2.5 (± 14.51)	-4.8 (± 15.27)	-4.6 (± 17.96)

Notes:

[106] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[107] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[108] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[109] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[110]			
Units: percent				
arithmetic mean (standard deviation)	-1.9 (± 12.49)			

Notes:
[110] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	Placebo v E4 2.5 mg
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9999
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.76
upper limit	6.23

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7691
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	2.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.78
upper limit	8.33

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6119
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.64
upper limit	3.14

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9548
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.46
upper limit	4.76

Secondary: Change in Serum Concentration of Protein-C from Baseline to Week 13

End point title	Change in Serum Concentration of Protein-C from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[111]	46[112]	53[113]	49[114]
Units: percent				
arithmetic mean (standard deviation)	-1.7 (± 14.53)	-2.0 (± 15.77)	-1.9 (± 15.51)	-2.5 (± 15.02)

Notes:

[111] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[112] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[113] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[114] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[115]			
Units: percent				
arithmetic mean (standard deviation)	-5.2 (± 14.11)			

Notes:

[115] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9774
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.91
upper limit	8.53

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6022
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	3.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	10.87

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9741
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.82
upper limit	8.53

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.884
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.23
upper limit	9.6

Secondary: Change in Serum Concentration of Free Protein-S from Baseline to Week 13

End point title	Change in Serum Concentration of Free Protein-S from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:
Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[116]	46[117]	53[118]	49[119]
Units: percent				
arithmetic mean (standard deviation)	-1.04 (± 12.227)	-3.00 (± 11.234)	-5.65 (± 10.148)	-9.20 (± 11.194)

Notes:
[116] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[117] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[118] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[119] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[120]			
Units: percent				
arithmetic mean (standard deviation)	-4.01 (± 13.473)			

Notes:
[120] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7798
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	7.39

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9693
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	6.63

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8984
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.86
upper limit	3.84

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0292
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.38
upper limit	-0.45

Secondary: Change in Serum Concentration of Factor VIII from Baseline to Week 13

End point title	Change in Serum Concentration of Factor VIII from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[121]	46[122]	53[123]	49[124]
Units: percent				
arithmetic mean (standard deviation)	4.3 (± 30.03)	-0.5 (± 35.28)	0.5 (± 31.80)	6.7 (± 46.46)

Notes:

[121] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[122] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[123] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[124] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[125]			
Units: percent				
arithmetic mean (standard deviation)	6.0 (± 29.97)			

Notes:

[125] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.304
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-9.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.67
upper limit	5.04

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2206
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-11.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.13
upper limit	4.05

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1189
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-12.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.33
upper limit	2.17

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8135
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.56
upper limit	9.96

Secondary: Change in Serum Concentration of Free Tissue Factor Pathway Inhibitor (TFPI) from Baseline to Week 13

End point title	Change in Serum Concentration of Free Tissue Factor Pathway Inhibitor (TFPI) from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[126]	46[127]	53[128]	49[129]
Units: ug/L				
arithmetic mean (standard deviation)	0.97 (± 8.357)	0.76 (± 8.347)	0.10 (± 10.928)	-3.05 (± 10.320)

Notes:

[126] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[127] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[128] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[129] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[130]			
Units: ug/L				
arithmetic mean (standard deviation)	0.54 (± 9.069)			

Notes:

[130] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6298
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-1.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.12
upper limit	2.28

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9916
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.84
upper limit	3.66

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9925
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	3.58

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2657
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.32
upper limit	1.33

Secondary: Change in Activated protein C sensitivity ratio (APCsr) (Endogenous Thrombin Potential [ETP] - Based) from Baseline to Week 13

End point title	Change in Activated protein C sensitivity ratio (APCsr) (Endogenous Thrombin Potential [ETP] - Based) from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[131]	0[132]	0[133]	0[134]
Units: Ratio				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[131] - Data for this factor are not yet available.

[132] - Data for this factor are not yet available.

[133] - Data for this factor are not yet available.

[134] - Data for this factor are not yet evaluable.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[135]			
Units: Ratio				
arithmetic mean (standard deviation)	()			

Notes:

[135] - Data for this factor are not yet available.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Serum Concentration of Osteocalcin from Baseline to Week 13

End point title	Change in Serum Concentration of Osteocalcin from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[136]	46[137]	53[138]	49[139]
Units: µg/L				
arithmetic mean (standard deviation)	2.93 (± 7.080)	-0.43 (± 5.967)	-0.63 (± 7.806)	0.08 (± 6.467)

Notes:

[136] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[137] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[138] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[139] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[140]			
Units: µg/L				
arithmetic mean (standard deviation)	2.44 (± 8.223)			

Notes:

[140] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.904
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.27
upper limit	4

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2154
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.59
upper limit	0.85

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1345
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.69
upper limit	0.53

Statistical analysis title	E4 15 mg vs Placebo
Comparison groups	E4 15 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0474
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-3.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.36
upper limit	-0.03

Secondary: Change in Serum Concentration of C-Terminal Telopeptide (CTX-1) from Baseline to Week 13

End point title	Change in Serum Concentration of C-Terminal Telopeptide (CTX-1) from Baseline to Week 13

End point description:

Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[141]	46[142]	53[143]	49[144]
Units: ng/L				
arithmetic mean (standard deviation)	-28.0 (± 181.90)	-83.3 (± 170.60)	-127.3 (± 171.11)	-95.3 (± 429.60)

Notes:

[141] - ITT N = 53
ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach
[142] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[143] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

[144] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[145]			
Units: ng/L				
arithmetic mean (standard deviation)	17.9 (± 200.84)			

Notes:

[145] - ITT set with baseline and week 13 data, last observation carried forward [LOCF] approach

Statistical analyses

Statistical analysis title	E4 2.5 mg vs Placebo
Comparison groups	E4 2.5 mg v Placebo

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9547
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-23.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-128.72
upper limit	82.19

Statistical analysis title	E4 5 mg vs Placebo
Comparison groups	E4 5 mg v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0711
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-101.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-209.51
upper limit	6.16

Statistical analysis title	E4 10 mg vs Placebo
Comparison groups	E4 10 mg v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0038
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-140.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-245.08
upper limit	-36.67

Statistical analysis title	E4 15 mg vs Placebo

Comparison groups	Placebo v E4 15 mg
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0634
Method	ANCOVA by Dunnett's test
Parameter estimate	Mean difference (final values)
Point estimate	-102.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-208.26
upper limit	4.05

Secondary: Number of Participants Who Experienced a Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced a Treatment-Emergent Adverse Event (TEAE)

End point description:

An AE is any untoward medical occurrence in a participant of a clinical trial, which does not necessarily have any causal relationship with the product under investigation. A treatment-emergent adverse event (TEAE) is defined as an AE with an onset that occurs after receiving study drug.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline to end of trial, a maximum of 119 days

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[146]	47[147]	54[148]	49[149]
Units: Participants	30	25	30	31

Notes:

[146] - SA set N = 52
SA set: All randomized participants who received at least 1 dose of study drug
[147] - SA set: All randomized participants who received at least 1 dose of study drug

[148] - SA set: All randomized participants who received at least 1 dose of study drug

[149] - SA set: All randomized participants who received at least 1 dose of study drug

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[150]			
Units: Participants	26			

Notes:

[150] - SA set: All randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Serious Adverse Event (SAE)

End point title	Number of Participants Who Experienced a Serious Adverse Event (SAE)

End point description:

A SAE was defined as an AE that met one or more of the following outcomes which were classified as serious:

• Results in death
• Is life-threatening (The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe.)
• Requires subject hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity
• Is a congenital birth defect
• Medically important condition
• Requires intervention to prevent one or more of the outcomes listed in the definition above

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline to end of trial, a maximum of 119 days

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[151]	47[152]	54[153]	49[154]
Units: Participants	0	0	0	2

Notes:

[151] - SA set N = 52
SA set: All randomized participants who received at least 1 dose of study drug
[152] - SA set: All randomized participants who received at least 1 dose of study drug

[153] - SA set: All randomized participants who received at least 1 dose of study drug

[154] - SA set: All randomized participants who received at least 1 dose of study drug

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[155]			
Units: Participants	1			

Notes:

[155] - SA set: All randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Treatment Related Adverse Event

End point title	Number of Participants Who Experienced a Treatment Related Adverse Event

End point description:

A treatment-related AE was defined as an AE related to the study drug or related to the study procedure as assessed by the principle investigator.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline to end of trial, a maximum of 119 days

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[156]	47[157]	54[158]	49[159]
Units: Participants				
Related to study drug	14	12	21	25
Related to study procedure	3	2	2	5

Notes:

[156] - SA set N = 52
SA set: All randomized participants who received at least 1 dose of study drug

[157] - SA set: All randomized participants who received at least 1 dose of study drug

[158] - SA set: All randomized participants who received at least 1 dose of study drug

[159] - SA set: All randomized participants who received at least 1 dose of study drug

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[160]			
Units: Participants				
Related to study drug	13			
Related to study procedure	0			

Notes:

[160] - SA set: All randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Clinically Significant Clinical Laboratory Measurement

End point title	Number of Participants Who Experienced a Clinically Significant Clinical Laboratory Measurement

End point description:

Laboratory measurements included hematology, chemistry and urinalysis.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline to end of trial, a maximum of 119 days

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[161]	47[162]	54[163]	49[164]
Units: Participants				
Aspartate aminotransferase increased	0	0	1	0
Blood cholesterol increased	0	0	0	1
Blood creatine phosphokinase increased	0	0	1	0
Blood triglycerides increased	0	0	0	1
Low density lipoprotein increased	0	0	0	1

Notes:

[161] - SA set N = 52
SA set: All randomized participants who received at least 1 dose of study drug

[162] - SA set: All randomized participants who received at least 1 dose of study drug

[163] - SA set: All randomized participants who received at least 1 dose of study drug

[164] - SA set: All randomized participants who received at least 1 dose of study drug

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[165]			
Units: Participants				
Aspartate aminotransferase increased	0			
Blood cholesterol increased	0			
Blood creatine phosphokinase increased	0			
Blood triglycerides increased	0			
Low density lipoprotein increased	0			

Notes:

[165] - SA set: All randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Endometrial Thickness at Each Study Visit

End point title	Mean Endometrial Thickness at Each Study Visit

End point description:

Endometrial thickness assessment was done by the investigator, gynaecologist or designee at each study visit, planned or unplanned.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Screening, Baseline, Week 5, Week 13, and Week 16

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44[166]	43[167]	49[168]	40[169]
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Screening	2.6 (± 1.00)	2.7 (± 0.96)	2.4 (± 1.05)	2.6 (± 1.00)
Baseline	2.7 (± 1.13)	2.4 (± 1.06)	2.5 (± 1.09)	2.7 (± 1.08)
Week 5	3.9 (± 1.86)	5.4 (± 3.13)	6.2 (± 3.07)	6.2 (± 3.94)
Week 13	4.5 (± 2.80)	5.5 (± 3.10)	6.3 (± 3.24)	7.9 (± 4.04)
Week 16	3.3 (± 1.62)	3.6 (± 2.02)	3.0 (± 0.93)	3.1 (± 2.04)

Notes:

[166] - Screening N = 44
Baseline N = 44
Week 5 N = 38
Week 13 N = 43
Week 16 N = 41

[167] - Screening N = 43
Baseline N = 43
Week 5 N = 39
Week 13 N = 42
Week 16 N = 40

[168] - Screening N = 49
Baseline N = 49
Week 5 N = 42
Week 13 N = 46
Week 16 N = 42

[169] - Screening N = 40
Baseline N = 40
Week 5 N = 36
Week 13 N = 38
Week 16 N = 38

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	49[170]			
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Screening	2.6 (± 1.01)			
Baseline	2.5 (± 1.11)			
Week 5	4.0 (± 2.49)			
Week 13	3.4 (± 2.10)			
Week 16	3.0 (± 1.58)			

Notes:

[170] - Screening N = 49
Baseline N = 49
Week 5 N = 41
Week 13 N = 48
Week 16 N = 44

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced Abnormal Uterine Bleeding at Each Study Visit

End point title	Number of Participants Who Experienced Abnormal Uterine Bleeding at Each Study Visit

End point description:

Abnormal uterine bleeding was defined as the occurrence of vaginal bleeding or spotting on a daily basis reported using the scale below:

1=Spotting: evidence of minimal blood loss requiring none or at most one pad, tampon or panty liner per day
2=Bleeding: evidence of blood loss requiring more than one pad, tampon or panty liner per day.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Screening to Week 16

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44[171]	43[172]	49[173]	40[174]
Units: Participants				
Screening	0	0	0	0
Baseline	0	0	0	0
Week 5	0	0	1	0
Week 13	4	2	7	9
Week 16	1	2	3	4

Notes:

[171] - Screening N = 44
Baseline N = 43
Week 5 N = 37
Week 13 N = 43
Week 16 N = 42

[172] - Screening N = 43
Baseline N = 43
Week 5 N = 39
Week 13 N = 42
Week 16 N = 41

[173] - Screening N = 49
Baseline N = 48
Week 5 N = 42

Week 13 N = 46
Week 16 N = 44
[174] - Screening N = 39
Baseline N = 39
Week 5 N = 35
Week 13 N = 38
Week 16 N = 39

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	49[175]			
Units: Participants				
Screening	0			
Baseline	0			
Week 5	2			
Week 13	2			
Week 16	0			

Notes:

[175] - Screening N = 48
Baseline N = 48
Week 5 N = 41
Week 13 N = 47
Week 16 N = 45

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Clinically Significant Physical Examination Measurement

End point title	Number of Participants Who Experienced a Clinically Significant Physical Examination Measurement

End point description:

The physical examination included an examination of general appearance, head, eyes, nose, throat, skin, neck, lungs, breasts, lymph nodes, abdomen, and the cardiovascular, musculoskeletal and neurological systems.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set. Data produced from the shift table analysis. Inclusive of all participants with baseline and week 13 data.

The number of participants per treatment group with available data varied for each system. The number of participants with available data in each arm is as follows:
2.5 mg E4: up to 51 participants
5 mg E4: up to 46 participants
10 mg E4: up to 50 participants
15 mg E4: up to 47 participants
Placebo: up to 54 participants

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[176]	47[177]	53[178]	49[179]
Units: Participants				
General appearance	0	0	0	0
Head	0	0	0	0
Eyes	0	0	0	0
Ears	0	0	0	0
Nose	0	0	0	0
Throat	0	0	0	0
Skin	1	0	0	0
Neck	0	0	0	0
Lungs	0	0	0	0
Lymph nodes	0	0	0	0
Abdomen	0	0	0	0
Cardiovascular	1	0	0	0
Musculoskeletal	0	0	0	0
Neurological	0	0	0	0

Notes:

[176] - SA set N = 52
SA set: All randomized participants who received at least 1 dose of study drug
[177] - SA set: All randomized participants who received at least 1 dose of study drug

[178] - SA set: All randomized participants who received at least 1 dose of study drug

[179] - SA set: All randomized participants who received at least 1 dose of study drug

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[180]			
Units: Participants				
General appearance	0			
Head	0			
Eyes	0			
Ears	0			
Nose	0			
Throat	0			
Skin	0			
Neck	0			
Lungs	0			
Lymph nodes	0			
Abdomen	0			
Cardiovascular	0			
Musculoskeletal	0			
Neurological	0			

Notes:

[180] - SA set: All randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Clinically Significant

Gynaecological Examination

End point title	Number of Participants Who Experienced a Clinically Significant Gynaecological Examination

End point description:

Gynecological examination included inspection of breast, adnexa, cervix, uterus, vagina and external genitalia.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set. Data produced from the shift table analysis. Inclusive of all participants with baseline and visit 5 (end of trial visit) data.

End point type	Secondary

End point timeframe:

Baseline and end of trial (up to a maximum of 119 days)

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[181]	47[182]	54[183]	49[184]
Units: Participants				
Breast	0	0	0	0
Adnexa	0	0	0	0
Cervix	0	0	0	0
Uterus	0	0	0	0
Vagina	0	0	0	0
External Genitalia	0	0	0	0

Notes:

[181] - Breast N = 40
Adnexa N = 39
Cervix N = 39
Uterus N = 38
Vagina N = 41
External Genitalia N = 41

[182] - Breast N = 39
Adnexa N = 38
Cervix N = 40
Uterus N = 40
Vagina N = 40
External Genitalia N = 40

[183] - Breast N = 42
Adnexa N = 42
Cervix N = 42
Uterus N = 39
Vagina N = 42
External Genitalia N = 42

[184] - Breast N = 39
Adnexa N = 39
Cervix N = 39
Uterus N = 39
Vagina N = 39
External Genitalia N = 39

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[185]			
Units: Participants				

Breast	0			
Adnexa	0			
Cervix	0			
Uterus	0			
Vagina	0			
External Genitalia	0			

Notes:

[185] - Breast N = 43
Adnexa N = 42
Cervix N = 43
Uterus N = 43
Vagina N = 43
External Genitalia N = 43

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants that Experienced a Clinically Significant Electrocardiogram (ECG) Result

End point title	Number of Participants that Experienced a Clinically Significant Electrocardiogram (ECG) Result

End point description:

The ECG interpretation scheme included the analysis of the morphology, rhythm, conduction, ST segment, PR, QRS, QT and QTc intervals, T waves, U waves and the presence or absence of any pathological changes.

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline to Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[186]	47[187]	54[188]	49[189]
Units: Participants	0	1	1	0

Notes:

[186] - SA set N = 52
SA set: All randomized participants who received at least 1 dose of study drug
[187] - SA set: All randomized participants who received at least 1 dose of study drug
[188] - SA set: All randomized participants who received at least 1 dose of study drug
[189] - SA set: All randomized participants who received at least 1 dose of study drug

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	55[190]			
Units: Participants	1			

Notes:

[190] - SA set: All randomized participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Body Mass Index (BMI) from Baseline to Week 13

End point title	Change in Body Mass Index (BMI) from Baseline to Week 13

End point description:

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[191]	46[192]	50[193]	47[194]
Units: kg/m2				
arithmetic mean (standard deviation)	0.12 (± 0.765)	0.28 (± 0.574)	0.33 (± 0.654)	0.11 (± 0.714)

Notes:

[191] - SA N: 52
Randomized participants, received ≥1 dose of study drug, with data at baseline and week 13

[192] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

[193] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

[194] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[195]			
Units: kg/m2				
arithmetic mean (standard deviation)	0.09 (± 0.618)			

Notes:

[195] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Blood Pressure from Baseline to Week 13

End point title	Change in Blood Pressure from Baseline to Week 13

End point description:

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[196]	46[197]	51[198]	47[199]
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic Blood Pressure	-0.24 (± 9.768)	4.67 (± 9.942)	1.49 (± 10.961)	6.06 (± 12.858)
Diastolic Blood Pressure	-0.25 (± 7.954)	2.74 (± 7.347)	1.08 (± 8.724)	1.36 (± 6.391)

Notes:

[196] - SA N: 52
Randomized participants, received ≥1 dose of study drug, with data at baseline and week 13
[197] - SA: All participants who received at least 1 dose of study drug with data at baseline and week 13
[198] - SA: All participants who received at least 1 dose of study drug with data at baseline and week 13
[199] - SA: All participants who received at least 1 dose of study drug with data at baseline and week 13

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[200]			
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic Blood Pressure	2.31 (± 10.522)			
Diastolic Blood Pressure	2.35 (± 8.294)			

Notes:

[200] - SA: All participants who received at least 1 dose of study drug with data at baseline and week 13

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pulse Rate from Baseline to Week 13

End point title	Change in Pulse Rate from Baseline to Week 13

End point description:

All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set.

End point type	Secondary

End point timeframe:

Baseline and Week 13

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[201]	46[202]	51[203]	47[204]
Units: beats/min				
arithmetic mean (standard deviation)	-1.43 (± 8.031)	1.04 (± 7.510)	0.18 (± 9.427)	-0.47 (± 10.032)

Notes:

[201] - SA N: 52
Randomized participants, received ≥1 dose of study drug, with data at baseline and week 13

[202] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

[203] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

[204] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	54[205]			
Units: beats/min				
arithmetic mean (standard deviation)	0.22 (± 8.316)			

Notes:

[205] - SA: All participants who recieved at least 1 dose of study drug with data at baseline and week 13

Statistical analyses

No statistical analyses for this end point

Secondary: Estetrol (E4) Concentrations in Plasma

End point title	Estetrol (E4) Concentrations in Plasma[206]

End point description:

Analyzed using the pharmacokinetic (PK) set: All participants who received at least one dose of study drug and had at least one post-baseline plasma sample collected. One participant was randomized to receive 2.5 mg but also received 10 mg by error. The participant was allocated to the highest dose received, 10 mg group, for the analysis in the PK set.

End point type	Secondary

End point timeframe:

Baseline, Week 5 and Week 13

Notes:

[206] - 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: PK analysis was only planned for participants receiving E4.

End point values	E4 2.5 mg	E4 5 mg	E4 10 mg	E4 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52[207]	47[208]	52[209]	47[210]
Units: nmol/L				
arithmetic mean (standard deviation)				
Week 5	1.710 (± 1.3752)	4.159 (± 4.2086)	6.599 (± 4.3100)	13.324 (± 9.6068)
Week 13	1.639 (± 1.8015)	3.593 (± 4.2321)	5.894 (± 5.2996)	8.645 (± 10.0393)

Notes:

[207] - PK: All participants with at least 1 post baseline sample of PK data
Week 5 N = 46
Week 13 N = 51

[208] - PK: All participants with at least 1 post baseline sample of PK data
Week 5 N = 43
Week 13 N = 46

[209] - PK: All participants with at least 1 post baseline sample of PK data
Week 5 N = 47
Week 13 N = 50

[210] - PK: All participants with at least 1 post baseline sample of PK data
Week 5 N = 45
Week 13 N = 46

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to end of study, a maximum of 119 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	E4 2.5 mg
Reporting group description:	
Estetrol (E4) 2.5 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 5 mg
Reporting group description:	
Estetrol (E4) 5 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 10 mg
Reporting group description:	
Estetrol (E4) 10 mg was administered orally via a capsule, once daily.	
Reporting group title	E4 15 mg
Reporting group description:	
Estetrol (E4) 15 mg was administered orally via a capsule, once daily.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered orally via a capsule, once daily.	

Serious adverse events	E4 2.5 mg	E4 5 mg	E4 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 47 (0.00%)	0 / 54 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 52 (0.00%)	0 / 47 (0.00%)	0 / 54 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 47 (0.00%)	0 / 54 (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

Intervertebral disc protrusion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 47 (0.00%)	0 / 54 (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

Serious adverse events	E4 15 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 49 (4.08%)	1 / 55 (1.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	E4 2.5 mg	E4 5 mg	E4 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 52 (57.69%)	25 / 47 (53.19%)	30 / 54 (55.56%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 52 (7.69%)	3 / 47 (6.38%)	4 / 54 (7.41%)
occurrences (all)	4	9	8
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	3 / 52 (5.77%)	4 / 47 (8.51%)	12 / 54 (22.22%)
occurrences (all)	3	9	24
Uterine haemorrhage			
subjects affected / exposed	3 / 52 (5.77%)	2 / 47 (4.26%)	4 / 54 (7.41%)
occurrences (all)	4	2	5
Breast pain			
subjects affected / exposed	3 / 52 (5.77%)	1 / 47 (2.13%)	5 / 54 (9.26%)
occurrences (all)	3	1	6
Endometrial hypertrophy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 47 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 52 (0.00%)	0 / 47 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 52 (1.92%)	1 / 47 (2.13%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 52 (7.69%)	0 / 47 (0.00%)	3 / 54 (5.56%)
occurrences (all)	5	0	4
Urinary tract infection			
subjects affected / exposed	0 / 52 (0.00%)	3 / 47 (6.38%)	0 / 54 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	1 / 47 (2.13%)	3 / 54 (5.56%)
occurrences (all)	0	1	3

Non-serious adverse events	E4 15 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 49 (63.27%)	26 / 55 (47.27%)	
Nervous system disorders			
Headache			

subjects affected / exposed	4 / 49 (8.16%)	6 / 55 (10.91%)	
occurrences (all)	8	9	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	10 / 49 (20.41%)	3 / 55 (5.45%)	
occurrences (all)	16	6	
Uterine haemorrhage			
subjects affected / exposed	4 / 49 (8.16%)	2 / 55 (3.64%)	
occurrences (all)	4	2	
Breast pain			
subjects affected / exposed	4 / 49 (8.16%)	1 / 55 (1.82%)	
occurrences (all)	4	1	
Endometrial hypertrophy			
subjects affected / exposed	3 / 49 (6.12%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 49 (2.04%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 49 (2.04%)	3 / 55 (5.45%)	
occurrences (all)	1	4	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 49 (4.08%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 49 (2.04%)	1 / 55 (1.82%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2016	•Exclusion criteria number 8 was updated to clarify that participants with glucose laboratory values outside the normal ranges and glycated hemoglobin above 7% were not allowed to participate in the trial. •Exclusion criteria number 9 was updated to only include participants who were in the low or moderate cardiovascular risk category according to the SCORE chart issued by the European Association for Cardiovascular Prevention and Rehabilitation. •Instructions were added in regards to progestin treatment, that had to be followed in case of occurrences of abnormal uterine bleeding or endometrial thickness ≥15 mm. •"Presence of endometrial hyperplasia" was added as a reason for premature discontinuation to emphasize that endometrial hyperplasia is an absolute reason for a participant's discontinuation. •The statistical model for the analysis of "vaginal bleeding associated with sexual activity" (logistic regression) was specified. •Two analysis populations were added to initially planned study populations, the modified intent-to-treat and the modified per-protocol set, to allow analyzing the primary objective in participants who did not receive any progestin therapy during E4/placebo treatment.
09 January 2017	•Exclusion criteria 9 was amended to use the atherosclerotic cardiovascular disease score recommended by the North American Menopause Society rather than the European SCORE to evaluate the eligibility of the participants. The goal was 2-fold: firstly, to use the most recent and robust epidemiological evidence and the most recent recommendations in the menopausal field, secondly to give the investigator an easier and more user-friendly tool to evaluate the cardiovascular risk, limiting at the maximum the risk of mistakes. •Analysis of covariance was performed instead of mixed effect model repeat measurement for the analysis of the efficacy endpoints.
14 March 2017	Ireland-specific amendment. •Exclusion criteria number 15 was updated to "Acute or chronic renal impairment, including severe renal impairment" and exclusion criteria number 24 was updated to include "porphyria", following a request from Ireland Competent Authorities.
28 April 2017	•The population of eligible individuals was expanded to include hysterectomized women, and the age limit was decreased from 45 years to 40 years. •The inclusion criteria for postmenopausal status was revised as it seemed clinically relevant to consider as postmenopausal the subjects presenting 6 months of spontaneous amenorrhea associated with an absence of ovarian function (translated in a circulating level of estradiol <20 pg/mL). •The exclusion criteria "participants with QTc prolongation (QTcB and QTcF values >450 msec)" was removed. •"Use of >1 ml/day of nicotine-containing liquid for electronic cigarette" was added as an exclusion criteria. •The use of clonidine was added to the list of prohibited anti-hot-flush treatments. •A new exclusion criteria was added to exclude participants treated with drugs that might affect the occurrence of vasomotor symptoms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported