Clinical trial results:
A Phase 2, Dose-ranging, 12-week, Randomized, Double-blind, Placebo-controlled, Parallel-group Study Evaluating the Efficacy and Safety of Three Formulations of Ultra-low Dose Estriol Vaginal Gel (0.005% Estriol Vaginal Gel, 0.002% Estriol Vaginal Gel, 0.0008% Estriol Vaginal Gel) for the Treatment of Vaginal Dryness in Postmenopausal Women with Vulvovaginal Atrophy.

Summary

EudraCT number	2015-005787-42
Trial protocol	SE CZ HU ES IT
Global end of trial date	10 May 2018

Results information

Result version number	v1 (current)
This version publication date	25 May 2019
First version publication date	25 May 2019

Trial information

Trial identification

Sponsor protocol code	ITFE-2092-C1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02967510
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ITF Research Pharma SLU
Sponsor organisation address	c/ San Rafael 3, Madrid, Spain, 28108
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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	10 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose was to evaluate the efficacy of 0.005%, 0.002%, and 0.0008% estriol vaginal gel and determine the minimal effective dose for the treatment of postmenopausal vaginal atrophy in women who report moderate to severe vaginal dryness as the most bothersome symptom.

Protection of trial subjects:

This study was conducted in accordance with the accepted version of the Declaration of Helsinki and all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States (US) Code of Federal Regulations (CFR), in compliance with International Council for Harmonization (ICH) good clinical practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted. Safety evaluations included adverse events monitoring, clinical laboratory assessments (hematology, blood chemistry, hormones and urinalysis), transvaginal ultrasound, endometrial biopsy and electrocardiogram (ECG).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 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	Spain: 47
Country: Number of subjects enrolled	Sweden: 65
Country: Number of subjects enrolled	Czech Republic: 97
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Italy: 33
Worldwide total number of subjects	283
EEA total number of subjects	283

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	183
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

447 subjects were screened, 164 failed screening and 283 were randomized.

Pre-assignment

Screening details:

A total of 283 subjects were randomized out of which 261 completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Estriol 0.005%

Arm description:

Subjects received 1 gram of Estriol 0.005% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Arm type	Experimental
Investigational medicinal product name	Estriol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Subjects received 1 gram of Estriol 0.005% vaginal gel using the supplied applicator.

Arm title	Estriol 0.002%

Arm description:

Subjects received 1 gram of Estriol 0.002% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Arm type	Experimental
Investigational medicinal product name	Estriol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Subjects received 1 gram of Estriol 0.002% vaginal gel using the supplied applicator.

Arm title	Estriol 0.0008%

Arm description:

Subjects received 1 gram of Estriol 0.0008% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Arm type	Experimental

Investigational medicinal product name	Estriol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Subjects received 1 gram of Estriol 0.0008% vaginal gel using the supplied applicator.

Arm title	Placebo

Arm description:

Subjects received matching placebo vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

Subjects received matching placebo vaginal gel using the supplied applicator.

Number of subjects in period 1	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%
Started	70	70	72
Completed	66	67	65
Not completed	4	3	7
Consent withdrawn by subject	1	-	5
Physician decision	-	-	1
Non-Compliance with Study Drug	1	-	-
Adverse Event	1	2	1
Unspecified	-	1	-
Lost to follow-up	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	Placebo
Started	71
Completed	63
Not completed	8
Consent withdrawn by subject	2
Physician decision	-
Non-Compliance with Study Drug	-
Adverse Event	3
Unspecified	1
Lost to follow-up	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Estriol 0.005%
Reporting group description:	
Subjects received 1 gram of Estriol 0.005% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	
Reporting group title	Estriol 0.002%
Reporting group description:	
Subjects received 1 gram of Estriol 0.002% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	
Reporting group title	Estriol 0.0008%
Reporting group description:	
Subjects received 1 gram of Estriol 0.0008% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	

Reporting group values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%
Number of subjects	70	70	72
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.5	61.9	62.2
standard deviation	± 7.43	± 6.87	± 7.05
Gender categorical			
Units: Subjects			
Female	70	70	72
Male	0	0	0

Reporting group values	Placebo	Total	
Number of subjects	71	283	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62.3		
standard deviation	± 7.24	-	
Gender categorical			
Units: Subjects			
Female	71	283	
Male	0	0	

End points

End points reporting groups

Reporting group title	Estriol 0.005%
Reporting group description:	
Subjects received 1 gram of Estriol 0.005% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	
Reporting group title	Estriol 0.002%
Reporting group description:	
Subjects received 1 gram of Estriol 0.002% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	
Reporting group title	Estriol 0.0008%
Reporting group description:	
Subjects received 1 gram of Estriol 0.0008% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.	

Primary: Change from Baseline to Week 12 in the Severity of Vaginal Dryness

End point title	Change from Baseline to Week 12 in the Severity of Vaginal Dryness
End point description:	
Percentage of Subjects with change from baseline to Week 12 in the severity of vaginal dryness was reported. Severity was defined as: 0= Absent, 1= Mild, 2= Moderate, 3= Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	68
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	21.4	19.1	18.6	13.2
Change from Baseline: -2	32.9	48.5	37.1	38.2
Change from Baseline: -1	37.1	23.5	28.6	27.9
Change from Baseline: 0	5.7	8.8	15.7	19.1
Change from Baseline: 1	2.9	0	0	1.5

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Primary: Change from Baseline to Week 12 in Vaginal pH	
End point title	Change from Baseline to Week 12 in Vaginal pH
End point description:	
Change from Baseline to Week 12 in Vaginal pH was reported. A decrease in pH compared to Baseline represents a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: pH				
least squares mean (standard error)	-1.03 (± 0.106)	-1.04 (± 0.108)	-0.95 (± 0.107)	-0.29 (± 0.108)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.031
upper limit	-0.444

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.051
upper limit	-0.458

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.951
upper limit	-0.369

Primary: Change from Baseline to Week 12 in the Proportion of Superficial Cells of the Vaginal Epithelium

End point title	Change from Baseline to Week 12 in the Proportion of Superficial Cells of the Vaginal Epithelium

End point description:

Change from Baseline to Week 12 in the proportion of superficial cells of the vaginal epithelium was reported. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	64	70	66
Units: ratio				
least squares mean (standard error)	0.24 (± 0.023)	0.17 (± 0.024)	0.19 (± 0.023)	0.02 (± 0.024)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.147
upper limit	0.278

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.213

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.097
upper limit	0.226

Primary: Change from Baseline to Week 12 in the Proportion of Parabasal Cells of the Vaginal Epithelium

End point title	Change from Baseline to Week 12 in the Proportion of Parabasal Cells of the Vaginal Epithelium

End point description:

Change from Baseline to Week 12 in the proportion of parabasal cells of the vaginal epithelium was reported. A decrease in proportion of parabasal cells compared to Baseline represents a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	64	70	66
Units: ratio				
least squares mean (standard error)	-0.54 (± 0.036)	-0.51 (± 0.037)	-0.47 (± 0.036)	-0.04 (± 0.038)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.603
upper limit	-0.4

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.572
upper limit	-0.365

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.531
upper limit	-0.331

Secondary: Change from Baseline to Week 12 in Severity of Dyspareunia

End point title	Change from Baseline to Week 12 in Severity of Dyspareunia

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of Dyspareunia was reported. Dyspareunia was only applicable in subjects who had experienced sexual activity with penetration since the previous study visit. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	31	41	32
Units: Percentage of subjects				
number (not applicable)				
Change from Baseline: -3	17.9	16.1	9.8	9.4
Change from Baseline: -2	23.1	22.6	39.0	34.4
Change from Baseline: -1	30.8	41.9	29.3	25.0
Change from Baseline: 0	25.6	16.1	12.2	28.1
Change from Baseline: 1	0	3.2	7.3	0
Change from Baseline: 2	2.6	0	2.4	3.1
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Pruritus or Itching

End point title	Change from Baseline to Week 12 in Severity of Pruritus or Itching

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of Pruritus or Itching was reported. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	2.9	7.4	5.7	5.8
Change from Baseline: -2	22.9	20.6	21.4	18.8
Change from Baseline: -1	25.7	29.4	28.6	29.0
Change from Baseline: 0	47.1	32.4	40.0	36.2
Change from Baseline: 1	0	5.9	2.9	7.2

Change from Baseline: 2	1.4	2.9	1.4	2.9
Change from Baseline: 3	0	1.5	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.348
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Burning

End point title	Change from Baseline to Week 12 in Severity of Burning

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of burning was reported. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	7.1	5.9	10.0	5.8
Change from Baseline: -2	31.4	30.9	25.7	27.5
Change from Baseline: -1	35.7	25.0	25.7	33.3
Change from Baseline: 0	25.7	35.3	37.1	29.0
Change from Baseline: 1	0	1.5	1.4	2.9
Change from Baseline: 2	0	1.5	0	1.4
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.122
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.188
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Dysuria

End point title	Change from Baseline to Week 12 in Severity of Dysuria

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of Dysuria was reported. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	0	1.5	1.4	1.4
Change from Baseline: -2	11.4	11.8	7.1	7.2
Change from Baseline: -1	25.7	27.9	24.3	21.7
Change from Baseline: 0	61.4	57.4	57.1	63.8
Change from Baseline: 1	1.4	1.5	10.0	0
Change from Baseline: 2	0	0	0	2.9
Change from Baseline: 3	0	0	0	2.9

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.393
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.432
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 12 in Global Symptom Score 1	
End point title	Change from Baseline to Week 12 in Global Symptom Score 1
End point description:	
Global Symptom Score 1 was defined as the sum of all 5 individual symptom scores at a given visit, and was calculated only when all 5 symptom scores had a response available. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	31	41	31
Units: units on a scale				
least squares mean (standard error)	-4.30 (± 0.425)	-4.78 (± 0.478)	-4.51 (± 0.412)	-4.54 (± 0.467)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.487

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.361
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.568
upper limit	1.09

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.522
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.188
upper limit	1.257

Secondary: Change from Baseline to Week 12 in Global Symptom Score 2

End point title	Change from Baseline to Week 12 in Global Symptom Score 2

End point description:

Change from baseline to Week 12 in Global Symptom Score 2. Global Symptom Score 2 was defined as the sum of all 4 individual symptom scores (excluding dyspareunia) at a given visit, and was calculated only when all 4 symptom scores had a response available. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	68
Units: units on a scale				
least squares mean (standard error)	-3.83 (± 0.231)	-3.78 (± 0.234)	-3.74 (± 0.233)	-3.27 (± 0.237)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.204
upper limit	0.079

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.158
upper limit	0.137

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.111
upper limit	0.16

Secondary: Change from Baseline to Week 12 in Severity of Pallor

End point title	Change from Baseline to Week 12 in Severity of Pallor

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of Pallor was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:
Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	4.3	7.4	1.4	1.4
Change from Baseline: -2	24.3	23.5	35.7	21.7
Change from Baseline: -1	44.3	45.6	35.7	26.1
Change from Baseline: 0	22.9	23.5	24.3	44.9
Change from Baseline: 1	4.3	0	2.9	5.8
Change from Baseline: 2	0	0	0	0
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Friability

End point title	Change from Baseline to Week 12 in Severity of Friability

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of Friability was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	2.9	2.9	2.9	4.3
Change from Baseline: -2	27.1	30.9	25.7	27.5
Change from Baseline: -1	37.1	32.4	44.3	29.0
Change from Baseline: 0	30.0	32.4	22.9	34.8
Change from Baseline: 1	1.4	0	4.3	4.3
Change from Baseline: 2	1.4	1.5	0	0
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.438
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.388
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Thinning or Flattening of Folds

End point title	Change from Baseline to Week 12 in Severity of Thinning or Flattening of Folds

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of thinning or flattening of folds was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	5.7	1.5	1.4	1.4
Change from Baseline: -2	25.7	26.5	32.9	8.7
Change from Baseline: -1	41.4	48.5	34.3	44.9
Change from Baseline: 0	24.3	20.6	27.1	37.7
Change from Baseline: 1	2.9	2.9	4.3	7.2
Change from Baseline: 2	0	0	0	0
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Presence of Petechiae

End point title	Change from Baseline to Week 12 in Severity of Presence of Petechiae

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of presence of Petechiae was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	2.9	1.5	0	2.9
Change from Baseline: -2	14.3	7.4	10.0	2.9
Change from Baseline: -1	37.1	33.8	32.9	18.8
Change from Baseline: 0	41.4	51.5	50.0	71.0
Change from Baseline: 1	4.3	5.9	7.1	4.3
Change from Baseline: 2	0	0	0	0
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.331
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 12 in Severity of Dry Mucosa

End point title	Change from Baseline to Week 12 in Severity of Dry Mucosa

End point description:

Percentage of subjects with change from baseline to Week 12 in severity of dry mucosa was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	68	70	69
Units: percentage of subjects				
number (not applicable)				
Change from Baseline: -3	11.4	19.1	20.0	13.0
Change from Baseline: -2	55.7	42.6	37.1	27.5
Change from Baseline: -1	24.3	29.4	32.9	27.5
Change from Baseline: 0	7.1	8.8	8.6	27.5
Change from Baseline: 1	1.4	0	1.4	4.3
Change from Baseline: 2	0	0	0	0
Change from Baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Vaginal Dryness

End point title	Change from Baseline to Week 3 in Severity of Vaginal Dryness

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of vaginal dryness was reported. Severity was defined as: 0= Absent, 1= Mild, 2= Moderate, 3= Severe. A decrease in score compared to Baseline represented a positive outcome.The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	66	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	8.8	12.1	11.8	4.4
Change from baseline: -2	33.8	19.7	32.4	38.2
Change from baseline: -1	41.2	50.0	38.2	38.2
Change from baseline: 0	11.8	18.2	16.2	16.2
Change from baseline: 1	4.4	0	1.5	2.9

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.176
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Dyspareunia

End point title	Change from Baseline to Week 3 in Severity of Dyspareunia

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of Dyspareunia was reported. Dyspareunia was only applicable in subjects who had experienced sexual activity with penetration since the previous study visit. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	37	27
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	3.0	10.3	10.8	7.4
Change from baseline: -2	21.2	13.8	27.0	25.9
Change from baseline: -1	33.3	37.9	37.8	37.0
Change from baseline: 0	39.4	20.7	21.6	25.9
Change from baseline: 1	0	13.8	0	3.7
Change from baseline: 2	3.0	3.4	2.7	0
Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106
Method	Wilcoxon Rank Sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	Wilcoxon Rank Sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.345
Method	Wilcoxon Rank Sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Pruritus or Itching	
End point title	Change from Baseline to Week 3 in Severity of Pruritus or Itching
End point description:	
Percentage of subjects with change from baseline to Week 3 in severity of Pruritus or Itching was reported. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome.The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline to Week 3	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	1.5	6.0	2.9	1.5
Change from baseline: -2	14.7	14.9	10.3	14.7
Change from baseline: -1	22.1	28.4	44.1	35.3
Change from baseline: 0	51.5	40.3	39.7	44.1
Change from baseline: 1	7.4	3.0	2.9	0
Change from baseline: 2	2.9	6.0	0	4.4
Change from baseline: 3	0	1.5	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.424
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.414
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Burning

End point title	Change from Baseline to Week 3 in Severity of Burning

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of Burning was reported. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N
(number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	4.4	3.0	5.9	0
Change from baseline: -2	16.2	25.4	20.6	23.5
Change from baseline: -1	39.7	26.9	29.4	30.9
Change from baseline: 0	39.7	41.8	42.6	41.2
Change from baseline: 1	0	1.5	1.5	2.9
Change from baseline: 2	0	1.5	0	1.5

Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Dysuria

End point title	Change from Baseline to Week 3 in Severity of Dysuria

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of Dysuria was reported. Symptom Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome.The ITT population defined as all randomized subjects. Here, N
(number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	0	0	1.5	0
Change from baseline: -2	7.4	11.9	4.4	8.8
Change from baseline: -1	20.6	23.9	20.6	13.2
Change from baseline: 0	67.6	58.2	70.6	70.6
Change from baseline: 1	4.4	4.5	2.9	4.4
Change from baseline: 2	0	0	0	0
Change from baseline: 3	0	1.5	0	2.9

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.133
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 3 in Global Symptom Score 1

End point title	Change from Baseline to Week 3 in Global Symptom Score 1

End point description:

Change from baseline to Week 3 in Global Symptom Score 1 was reported. Global Symptom Score 1 was defined as the sum of all 5 individual symptom scores at a given visit, and was calculated only when all 5 symptom scores had a response available. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	37	27
Units: units on a scale				
least squares mean (standard error)	-2.99 (± 0.483)	-2.86 (± 0.520)	-4.37 (± 0.454)	-3.73 (± 0.527)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.669
upper limit	2.153

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.877
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.611
upper limit	2.361

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.178
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.009
upper limit	0.728

Secondary: Change from Baseline to Week 3 in Global Symptom Score 2

End point title	Change from Baseline to Week 3 in Global Symptom Score 2

End point description:

Change from baseline to Week 3 in Global Symptom Score 2 was reported. Global Symptom Score 2 was defined as the sum of all 4 individual symptom scores (excluding dyspareunia) at a given visit, and was calculated only when all 4 symptom scores had a response available. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	66	68	68
Units: units on a scale				
least squares mean (standard error)	-2.76 (± 0.251)	-2.82 (± 0.254)	-3.20 (± 0.253)	-2.60 (± 0.255)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.323
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.854
upper limit	0.531

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.917
upper limit	0.484

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.084

Secondary: Change from Baseline to Week 3 in Severity of Pallor

End point title	Change from Baseline to Week 3 in Severity of Pallor

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of Pallor was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of
subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	4.4	3.0	1.5	0
Change from baseline: -2	20.6	20.9	20.6	8.8
Change from baseline: -1	27.9	29.9	35.3	27.9
Change from baseline: 0	45.6	44.8	42.6	55.9
Change from baseline: 1	1.5	1.5	0	7.4
Change from baseline: 2	0	0	0	0
Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Friability	
End point title	Change from Baseline to Week 3 in Severity of Friability
End point description:	
Percentage of subjects with change from baseline to Week 3 in severity of Friability was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome.The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline to Week 3	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	2.9	3.0	1.5	0
Change from baseline: -2	20.6	16.4	19.1	13.2
Change from baseline: -1	42.6	37.3	36.8	35.3
Change from baseline: 0	32.4	37.3	39.7	47.1
Change from baseline: 1	1.5	4.5	2.9	4.4
Change from baseline: 2	0	1.5	0	0
Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Thinning or Flattening of Folds

End point title	Change from Baseline to Week 3 in Severity of Thinning or Flattening of Folds

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of Thinning or Flattening of Folds was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	1.5	1.5	0	0
Change from baseline: -2	17.6	13.4	14.7	7.4
Change from baseline: -1	47.1	52.2	45.6	23.5
Change from baseline: 0	29.4	31.3	38.2	63.2
Change from baseline: 1	4.4	1.5	1.5	5.9
Change from baseline: 2	0	0	0	0
Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Presence of Petechiae

End point title	Change from Baseline to Week 3 in Severity of Presence of Petechiae

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of presence of Petechiae was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	2.9	0	0	0
Change from baseline: -2	11.8	9.0	8.8	4.4
Change from baseline: -1	33.8	26.9	32.4	10.3
Change from baseline: 0	45.6	61.2	55.9	79.4
Change from baseline: 1	4.4	3.0	1.5	4.4
Change from baseline: 2	1.5	0	1.5	1.5
Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from Baseline to Week 3 in Severity of Dry Mucosa

End point title	Change from Baseline to Week 3 in Severity of Dry Mucosa

End point description:

Percentage of subjects with change from baseline to Week 3 in severity of dry mucosa was reported. Sign Scores at each visit: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe. A decrease in score compared to Baseline represented a positive outcome. The ITT population defined as all randomized subjects. Here, N
(number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: percentage of subjects				
number (not applicable)				
Change from baseline: -3	5.9	11.9	8.8	4.4
Change from baseline: -2	42.6	29.9	38.2	25.0
Change from baseline: -1	32.4	44.8	30.9	29.4
Change from baseline: 0	17.6	13.4	22.1	38.2
Change from baseline: 1	1.5	0	0	2.9
Change from baseline: 2	0	0	0	0
Change from baseline: 3	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Secondary: Change from Baseline to Week 3 in Vaginal pH

End point title	Change from Baseline to Week 3 in Vaginal pH

End point description:

Change from baseline to Week 3 in Vaginal pH was reported. A decrease in pH compared to Baseline represents a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	67	68	68
Units: pH				
least squares mean (standard error)	-1.03 (± 0.095)	-0.97 (± 0.096)	-0.88 (± 0.095)	-0.22 (± 0.096)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.071
upper limit	-0.548

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.013
upper limit	-0.484

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.916
upper limit	-0.397

Secondary: Change from Baseline to Week 3 in Proportion of Superficial Cells of the Vaginal Epithelium

End point title	Change from Baseline to Week 3 in Proportion of Superficial Cells of the Vaginal Epithelium

End point description:

Change from baseline to Week 3 in proportion of superficial cells of the vaginal epithelium was reported. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 3

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	68	61
Units: ratio				
least squares mean (standard error)	0.48 (± 0.035)	0.43 (± 0.036)	0.38 (± 0.035)	0.04 (± 0.037)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.337
upper limit	0.535

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.291
upper limit	0.494

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.245
upper limit	0.439

Secondary: Change from Baseline to Week 3 in Proportion of Parabasal Cells of the Vaginal Epithelium

End point title	Change from Baseline to Week 3 in Proportion of Parabasal Cells of the Vaginal Epithelium

End point description:

Change from baseline to Week 3 in proportion of parabasal cells of the vaginal epithelium was reported. A decrease in proportion of parabasal cells compared to Baseline represents a positive outcome. The ITT population defined as all randomized subjects. Here, N (number of subjects analyzed) defined as number of subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe: Baseline to Week 3	

End point values	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	61	68	61
Units: ratio				
least squares mean (standard error)	-0.55 (± 0.037)	-0.57 (± 0.037)	-0.48 (± 0.036)	-0.08 (± 0.038)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Estriol 0.005% v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.575
upper limit	-0.371

Statistical analysis title	Statistical analysis 2
Comparison groups	Estriol 0.002% v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.592
upper limit	-0.383

Statistical analysis title	Statistical analysis 3
Comparison groups	Estriol 0.0008% v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 20 Weeks

Adverse event reporting additional description:

The Safety population included all randomized subjects who received at least 1 dose of study treatment. Data for treatment-emergent adverse events is presented here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Estriol 0.005%

Reporting group description:

Subjects received 1 gram of Estriol 0.005% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Reporting group title	Estriol 0.002%

Reporting group description:

Subjects received 1 gram of Estriol 0.002% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Reporting group title	Estriol 0.0008%

Reporting group description:

Subjects received 1 gram of Estriol 0.0008% vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo vaginal gel administered daily for Weeks 1-3. After 21 days of daily administration, treatment continued with twice-weekly administration up to Week 12.

Serious adverse events	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (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	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 71 (4.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Estriol 0.005%	Estriol 0.002%	Estriol 0.0008%
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 70 (20.00%)	11 / 69 (15.94%)	15 / 72 (20.83%)

Vascular disorders			
Flushing			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast inflammation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Ovarian cyst			
subjects affected / exposed	2 / 70 (2.86%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	2	0	0
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	4 / 70 (5.71%)	3 / 69 (4.35%)	4 / 72 (5.56%)
occurrences (all)	5	4	4
Animal bite			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Neck injury			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Radius fracture			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Hyperchlorhydria			

subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Loose tooth			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Cystitis			

subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	2 / 72 (2.78%)
occurrences (all)	0	1	3
Gastroenteritis viral			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	1 / 72 (1.39%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	1 / 70 (1.43%)	2 / 69 (2.90%)	3 / 72 (4.17%)
occurrences (all)	1	2	3
Pharyngitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Vulval abscess			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	20 / 71 (28.17%)		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast inflammation			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Ovarian cyst			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Vulvovaginal burning sensation			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Vulvovaginal pruritus			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	4		
Animal bite			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Neck injury			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Radius fracture			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Road traffic accident			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hyperchlorhydria			

subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Loose tooth			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Cystitis			

subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Vulval abscess			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2017	The major changes to amendment was: to clarify that a negative mammogram at Screening or a documented negative mammogram within 9 months of randomization was required; to clarify that for the subjects being re-screened within 1 month of a previous screen failure, the invasive procedures of biopsy and Factor V Leiden were not to be repeated, and the data from the Screening Visit were to be used again for the re-screened subject; to modify the endometrial biopsy section to clarify to Investigators how bleeding samples were to be analyzed, by adding the text: "If hyperplasia is diagnosed by the single safety reader for the subject who has bled while on study drug, this diagnosis be maintained for the efficacy evaluation and the slides become part of the slide set given to the 2 other pathologists for reading".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported