



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | MIT-Do0001-C201 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 260 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | E4 2.5 mg |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | E4 5 mg |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|----------|
| Arm title | E4 10 mg |
|------------------|----------|

Arm description:

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

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

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

| | |
|------------------|----------|
| Arm title | E4 15 mg |
|------------------|----------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

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

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

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

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 260 participants were randomized to treatment groups, but 3 participants did not receive study drug. Only participants who received study drug are included in the baseline period.

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

| | |
|--|---|
| End point title | Change in Weekly Frequency of Moderate to Severe Vasomotor Symptoms (VMS) from Baseline to Week 4 |
| End point description: The severity scoring system of VMS was documented by the participants in the participant's diary using the following scores: None (0) = no VMS symptoms Mild (1) = Sensation of heat without sweating Moderate (2) = Sensation of heat with sweating. Able to continue activity Severe (3) = Sensation of heat with sweating. Causes cessation of activity The weekly frequency of moderate to severe VMS at baseline and week 4 is defined as the total number of all recorded moderate to severe VMS experienced during the 7 day periods days -7 to -1 (baseline) and days 22 to 28 (week 4), respectively. Change = total No. of moderate & severe VMS at week 4 - total No. of moderate & severe VMS at baseline. A negative change from baseline score indicates a reduction in the frequency of moderate to severe VMS per week. Reported value are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Primary |
| End point timeframe: Baseline and Week 4 | |

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

Notes:

[1] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

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

End point description:

The severity scoring system of VMS was documented by the participants in the participants diary using the following scores:

None (0) = no VMS symptoms

Mild (1) = Sensation of heat without sweating

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

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

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

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline and Week 12 | |

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

Notes:

[6] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

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

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

End point description:

The severity scoring system of VMS was documented by the participants in the participants diary using the following scores:

None (0) = no VMS symptoms

Mild (1) = Sensation of heat without sweating

Moderate (2) = Sensation of heat with sweating. Able to continue activity

Severe (3) = Sensation of heat with sweating. Causes cessation of activity

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

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Week 4

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

Notes:

[11] - ITT N = 53

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

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

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

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

| | | | | |
|------------------|---------|--|--|--|
| End point values | Placebo | | | |
|------------------|---------|--|--|--|

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

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

End point description:

The severity scoring system of VMS was documented by the participants in the participants diary using the following scores:

None (0) = no VMS symptoms

Mild (1) = Sensation of heat without sweating

Moderate (2) = Sensation of heat with sweating. Able to continue activity

Severe (3) = Sensation of heat with sweating. Causes cessation of activity

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

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Week 12

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

Notes:

[16] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

to Week 13

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

End point description:

The following GSM symptoms were assessed:

Vaginal dryness

Vaginal and/or irritation/itching

Dysuria

Vaginal pain associated with sexual activity

These GSM symptoms were graded by the participants using the following scale: [0] none, [1] mild, [2] moderate, or [3] severe. A negative change from baseline score indicates improvement in symptoms.

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

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

Notes:

[21] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

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

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

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

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

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

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

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

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Dysuria: E4 15 mg vs Placebo |
|-----------------------------------|------------------------------|

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

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

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

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

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

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

| | |
|---|---|
| End point title | Change in Vaginal Bleeding Associated with Sexual Activity from Baseline to Week 13 |
| End point description: | |
| Vaginal bleeding (a genitourinary syndrome of menopause [GSM]) associated with sexual activity was documented using 3 categories: [0] absent, [1] present, or not applicable. | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 13 | |

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

Notes:

[26] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|--|--|
| End point title | Change in Menopause Rating Scale (MRS) Score from Baseline to Week 5 |
| End point description: | |
| MRS consists of 11 items (severity expressed in 0 to 4 points in each item). The total score of the MRS ranges between 0 (asymptomatic) to 44 (highest degree of complaints). A negative change from baseline indicates an improvement in symptoms. | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 5 | |

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

Notes:

[31] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

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

Notes:

[36] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | E4 15 mg vs Placebo |
|-----------------------------------|---------------------|

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

Secondary: Change in Vaginal pH from Baseline to Week 13

| | |
|---|---|
| End point title | Change in Vaginal pH from Baseline to Week 13 |
| End point description: | Vaginal pH was performed on-site by an investigator or qualified site personnel using a standardized vaginal pH paper test. |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 13 |

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

Notes:

[41] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

End point description:

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

MI = % parabasal cells, % intermediate cells, % superficial cells.

The vaginal MV is calculated as follows:

MV = 0.0 x parabasal cells [%] + 0.5 x intermediate cells [%] + 1.0 x superficial cells [%]

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

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

Notes:

[46] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|---|
| End point title | Change in Serum Concentration of Triglycerides from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[51] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|--|
| End point title | Change in Serum Concentration of High Density Lipoprotein (HDL) Cholesterol from Baseline to Week 13 |
| End point description: | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |

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

Notes:

[56] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

Cholesterol from Baseline to Week 13

| | |
|---|---|
| End point title | Change in Serum Concentration of Low Density Lipoprotein (LDL) Cholesterol from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[61] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

Secondary: Change in Total Cholesterol from Baseline to Week 13

| | |
|---|--|
| End point title | Change in Total Cholesterol from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[66] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | E4 15 mg vs Placebo |
|-----------------------------------|---------------------|

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

Secondary: Change in Fasting Glucose from Baseline to Week 13

| | |
|------------------------|---|
| End point title | Change in Fasting Glucose from Baseline to Week 13 |
| End point description: | Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 13 |

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

Notes:

[71] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

Secondary: Change in Insulin Levels from Baseline to Week 13

| | |
|------------------------|---|
| End point title | Change in Insulin Levels from Baseline to Week 13 |
| End point description: | Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 13 |

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

Notes:

[76] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|---|
| End point title | Change in Serum Concentration of Glycated Hemoglobin from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[81] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|--|
| End point title | Change in Homeostatis Model Assessment-Estimated Insulin Resistance (HOMA-IR) from Baseline to Week 13 |
| End point description: | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |

End point timeframe:
Baseline and Week 13

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

Notes:

[86] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

Baseline to Week 13

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

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

Notes:

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|--|
| End point title | Change in Serum Concentration of D-dimers from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[96] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | E4 15 mg vs Placebo |
|-----------------------------------|---------------------|

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

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

| | |
|------------------------|---|
| End point title | Change in Serum Concentration of Sex-Hormone Binding Globulin from Baseline to Week 13 |
| End point description: | Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 13 |

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

Notes:

[101] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

| | |
|------------------------|---|
| End point title | Change in Serum Concentration of Antithrombin from Baseline to Week 13 |
| End point description: | Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 13 |

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

Notes:

[106] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

| | |
|---|---|
| Secondary: Change in Serum Concentration of Protein-C from Baseline to Week 13 | |
| End point title | Change in Serum Concentration of Protein-C from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[111] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|--|
| End point title | Change in Serum Concentration of Free Protein-S from Baseline to Week 13 |
| End point description: | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |

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

Notes:

[116] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|---|
| End point title | Change in Serum Concentration of Factor VIII from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[121] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

| | |
|---|---|
| End point title | Change in Serum Concentration of Free Tissue Factor Pathway Inhibitor (TFPI) from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[126] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

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

| | |
|---|--|
| End point title | Change in Activated protein C sensitivity ratio (APCsr) (Endogenous Thrombin Potential [ETP] - Based) from Baseline to Week 13 |
| End point description: | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 13 | |

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

Notes:

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

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

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

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

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

Notes:

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

Statistical analyses

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

| | |
|---|---|
| End point title | Change in Serum Concentration of Osteocalcin from Baseline to Week 13 |
| End point description: | |
| Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 13 | |

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

Notes:

[136] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

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

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

| | |
|---|--|
| End point title | Change in Serum Concentration of C-Terminal Telopeptide (CTX-1) from Baseline to Week 13 |
| End point description: Reported values are for the intent-to-treat (ITT) analysis set, which is inclusive of all participants who received at least one dose of study drug on the planned treatment. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 13 | |

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

Notes:

[141] - ITT N = 53

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

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

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

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

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

Notes:

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

Statistical analyses

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

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

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

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

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | E4 15 mg vs Placebo |
|-----------------------------------|---------------------|

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

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

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to end of trial, a maximum of 119 days

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

Notes:

[146] - SA set N = 52

SA set: All randomized participants who received at least 1 dose of study drug

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to end of trial, a maximum of 119 days

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

Notes:

[151] - SA set N = 52

SA set: All randomized participants who received at least 1 dose of study drug

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to end of trial, a maximum of 119 days

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

Notes:

[156] - SA set N = 52

SA set: All randomized participants who received at least 1 dose of study drug

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Laboratory measurements included hematology, chemistry and urinalysis.

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to end of trial, a maximum of 119 days

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

Notes:

[161] - SA set N = 52

SA set: All randomized participants who received at least 1 dose of study drug

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Endometrial Thickness at Each Study Visit

| | |
|---|--|
| End point title | Mean Endometrial Thickness at Each Study Visit |
| End point description: | |
| Endometrial thickness assessment was done by the investigator, gynaecologist or designee at each study visit, planned or unplanned. | |
| All safety outcomes were analyzed using the safety analysis (SA) set: The SA set differs from the intent-to-treat (ITT) set as one participant randomized to the 2.5 mg E4 group received 10 mg by error. Therefore, the participant was allocated to the highest dose received, the 10 mg group, for analysis in the SA set. | |
| End point type | Secondary |
| End point timeframe: | |
| Screening, Baseline, Week 5, Week 13, and Week 16 | |

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

Notes:

[166] - Screening N = 44

Baseline N = 44

Week 5 N = 38

Week 13 N = 43

Week 16 N = 41

[167] - Screening N = 43

Baseline N = 43

Week 5 N = 39

Week 13 N = 42

Week 16 N = 40

[168] - Screening N = 49

Baseline N = 49

Week 5 N = 42

Week 13 N = 46

Week 16 N = 42

[169] - Screening N = 40

Baseline N = 40

Week 5 N = 36

Week 13 N = 38

Week 16 N = 38

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

Notes:

[170] - Screening N = 49

Baseline N = 49

Week 5 N = 41

Week 13 N = 48

Week 16 N = 44

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

2=Bleeding: evidence of blood loss requiring more than one pad, tampon or panty liner per day.

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening to Week 16

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

Notes:

[171] - Screening N = 44

Baseline N = 43

Week 5 N = 37

Week 13 N = 43

Week 16 N = 42

[172] - Screening N = 43

Baseline N = 43

Week 5 N = 39

Week 13 N = 42

Week 16 N = 41

[173] - Screening N = 49

Baseline N = 48

Week 5 N = 42

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

The number of participants per treatment group with available data varied for each system. The number of participants with available data in each arm is as follows:

2.5 mg E4: up to 51 participants
 5 mg E4: up to 46 participants
 10 mg E4: up to 50 participants
 15 mg E4: up to 47 participants
 Placebo: up to 54 participants

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

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

Notes:

[176] - SA set N = 52

SA set: All randomized participants who received at least 1 dose of study drug

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Clinically Significant

Gynaecological Examination

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[181] - Breast N = 40

Adnexa N = 39

Cervix N = 39

Uterus N = 38

Vagina N = 41

External Genitalia N = 41

[182] - Breast N = 39

Adnexa N = 38

Cervix N = 40

Uterus N = 40

Vagina N = 40

External Genitalia N = 40

[183] - Breast N = 42

Adnexa N = 42

Cervix N = 42

Uterus N = 39

Vagina N = 42

External Genitalia N = 42

[184] - Breast N = 39

Adnexa N = 39

Cervix N = 39

Uterus N = 39

Vagina N = 39

External Genitalia N = 39

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

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

Notes:

[185] - Breast N = 43

Adnexa N = 42

Cervix N = 43

Uterus N = 43

Vagina N = 43

External Genitalia N = 43

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 13

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

Notes:

[186] - SA set N = 52

SA set: All randomized participants who received at least 1 dose of study drug

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

| End point values | E4 2.5 mg | E4 5 mg | E4 10 mg | E4 15 mg |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 ^[191] | 46 ^[192] | 50 ^[193] | 47 ^[194] |
| Units: kg/m ² | | | | |
| arithmetic mean (standard deviation) | 0.12 (± 0.765) | 0.28 (± 0.574) | 0.33 (± 0.654) | 0.11 (± 0.714) |

Notes:

[191] - SA N: 52

Randomized participants, received ≥1 dose of study drug, with data at baseline and week 13

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

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

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

| End point values | Placebo | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 ^[195] | | | |
| Units: kg/m ² | | | | |
| arithmetic mean (standard deviation) | 0.09 (± 0.618) | | | |

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Blood Pressure from Baseline to Week 13

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 13

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

Notes:

[196] - SA N: 52

Randomized participants, received ≥1 dose of study drug, with data at baseline and week 13

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pulse Rate from Baseline to Week 13

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
Baseline and Week 13

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

Notes:

[201] - SA N: 52

Randomized participants, received ≥1 dose of study drug, with data at baseline and week 13

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

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

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Estetrol (E4) Concentrations in Plasma

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 5 and Week 13

Notes:

[206] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK analysis was only planned for participants receiving E4.

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

Notes:

[207] - PK: All participants with at least 1 post baseline sample of PK data

Week 5 N = 46

Week 13 N = 51

[208] - PK: All participants with at least 1 post baseline sample of PK data

Week 5 N = 43

Week 13 N = 46

[209] - PK: All participants with at least 1 post baseline sample of PK data

Week 5 N = 47

Week 13 N = 50

[210] - PK: All participants with at least 1 post baseline sample of PK data

Week 5 N = 45

Week 13 N = 46

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of study, a maximum of 119 days

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | E4 2.5 mg |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | E4 5 mg |
|-----------------------|---------|

Reporting group description:

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

| | |
|-----------------------|----------|
| Reporting group title | E4 10 mg |
|-----------------------|----------|

Reporting group description:

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

| | |
|-----------------------|----------|
| Reporting group title | E4 15 mg |
|-----------------------|----------|

Reporting group description:

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

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

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

| | | | |
|---|----------------|----------------|----------------|
| Intervertebral disc protrusion subjects affected / exposed | 0 / 52 (0.00%) | 0 / 47 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 26 July 2016 | <ul style="list-style-type: none">•Exclusion criteria number 8 was updated to clarify that participants with glucose laboratory values outside the normal ranges and glycated hemoglobin above 7% were not allowed to participate in the trial.•Exclusion criteria number 9 was updated to only include participants who were in the low or moderate cardiovascular risk category according to the SCORE chart issued by the European Association for Cardiovascular Prevention and Rehabilitation.•Instructions were added in regards to progestin treatment, that had to be followed in case of occurrences of abnormal uterine bleeding or endometrial thickness ≥ 15 mm.•"Presence of endometrial hyperplasia" was added as a reason for premature discontinuation to emphasize that endometrial hyperplasia is an absolute reason for a participant's discontinuation.•The statistical model for the analysis of "vaginal bleeding associated with sexual activity" (logistic regression) was specified.•Two analysis populations were added to initially planned study populations, the modified intent-to-treat and the modified per-protocol set, to allow analyzing the primary objective in participants who did not receive any progestin therapy during E4/placebo treatment. |
| 09 January 2017 | <ul style="list-style-type: none">•Exclusion criteria 9 was amended to use the atherosclerotic cardiovascular disease score recommended by the North American Menopause Society rather than the European SCORE to evaluate the eligibility of the participants. The goal was 2-fold: firstly, to use the most recent and robust epidemiological evidence and the most recent recommendations in the menopausal field, secondly to give the investigator an easier and more user-friendly tool to evaluate the cardiovascular risk, limiting at the maximum the risk of mistakes.•Analysis of covariance was performed instead of mixed effect model repeat measurement for the analysis of the efficacy endpoints. |
| 14 March 2017 | <p>Ireland-specific amendment.</p> <ul style="list-style-type: none">•Exclusion criteria number 15 was updated to "Acute or chronic renal impairment, including severe renal impairment" and exclusion criteria number 24 was updated to include "porphyria", following a request from Ireland Competent Authorities. |
| 28 April 2017 | <ul style="list-style-type: none">•The population of eligible individuals was expanded to include hysterectomized women, and the age limit was decreased from 45 years to 40 years.•The inclusion criteria for postmenopausal status was revised as it seemed clinically relevant to consider as postmenopausal the subjects presenting 6 months of spontaneous amenorrhea associated with an absence of ovarian function (translated in a circulating level of estradiol < 20 pg/mL).•The exclusion criteria "participants with QTc prolongation (QTcB and QTcF values > 450 msec)" was removed.•"Use of > 1 ml/day of nicotine-containing liquid for electronic cigarette" was added as an exclusion criteria.•The use of clonidine was added to the list of prohibited anti-hot-flush treatments.•A new exclusion criteria was added to exclude participants treated with drugs that might affect the occurrence of vasomotor symptoms. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported