



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | MIT-Do001-C301 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Estetra SRL |
| Sponsor organisation address | Rue Saint-Georges 5, Liege, Belgium, 4000 |
| Public contact | Clinical Study Leader, Estetra SRL, clinical.trials@estetra.com |
| Scientific contact | Clinical Study Leader, Estetra SRL, clinical.trials@estetra.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 February 2024 |
| Is this the analysis of the primary completion data? | No |
| <hr/> | |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 February 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Arms 1-3:

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

Arm 4:

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

Protection of trial subjects:

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

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

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

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

Background therapy:

None.

Evidence for comparator:

Not applicable.

DEFINITIONS USED IN THIS DATA RECORD:

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

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

(*) Efficacy Study Part only.

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

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

ABBREVIATIONS

Hx, hysterectomized
NH, non-hysterectomized

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1551 |
| From 65 to 84 years | 11 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Postmenopausal women aged 40-65 y seeking treatment for the relief of VMS associated with menopause (N=4502) were screened according to study inclusion and exclusion criteria:

- Efficacy Study Part: ≥ 7 moderate to severe VMS/day or ≥ 50 moderate to severe VMS/week.
- Safety Study Part: non hysterectomized; ≥ 1 moderate to severe VMS/week.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

Efficacy Study Part (ESP, Arms 1, 2, 3): randomized, double blind;

Safety Study Part (SSP, Arm 4): open-label.

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | E4 15 mg |

Arm description:

Efficacy Study Part: randomized, double-blind.

Estetrol monohydrate 15 mg (E4 15 mg), equivalent to estetrol 14.2 mg.

The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

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

Dosage and administration details:

Efficacy Study Part: randomized, double-blind.

Estetrol monohydrate 15 mg (E4 15 mg), equivalent to estetrol 14.2 mg.

The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

| | |
|------------------|----------|
| Arm title | E4 20 mg |
|------------------|----------|

Arm description:

Efficacy Study Part: randomized, double-blind.

Estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg.

The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

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

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

Dosage and administration details:

Efficacy Study Part: randomized, double-blind.

Estetrol monohydrate 20 mg (E4 20 mg), equivalent to estetrol 18.9 mg.

The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

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

Arm description:

Efficacy Study Part: randomized, double-blind.

Placebo, film-coated tablet, with no active substance.

The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

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

Dosage and administration details:

Efficacy Study Part: randomized, double-blind.

Film coated tablet, with no active substance.

The study drug was to be taken once a day for up to 13 weeks, at approximately the same time each day.

| | |
|------------------|----------------------|
| Arm title | E4 20 mg + P4 100 mg |
|------------------|----------------------|

Arm description:

Safety Study Part: open-label.

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

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

Dosage and administration details:

Safety Study part: open-label arm.

All subjects received E4 20 mg, equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg).

The study drugs were to be taken once a day for up to 53 weeks, at approximately the same time each day.

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

Dosage and administration details:

Safety Study Part: open-label arm.

All subjects received E4 20 mg, equivalent to estetrol 18.9 mg, in combination with Progesterone 100 mg (P4 100 mg) continuously for up to 53 weeks.

The study drugs were to be taken once a day for up to 53 weeks, at approximately the same time each day.

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

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

Baseline characteristics

Reporting groups

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

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

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

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

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

| | | | |
|--------------------|-------------|---|--|
| standard deviation | ± 4.183 | - | |
|--------------------|-------------|---|--|

End points

End points reporting groups

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

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

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

End point description:

Efficacy Study Part

The weekly frequency of moderate to severe VMS at baseline is defined as the sum of all recorded moderate to severe VMS experienced during the last 7 consecutive days prior randomization.

The weekly frequency of moderate to severe VMS at Week 4 is defined as the sum of all recorded moderate to severe VMS experienced during Week 4.

(VMS=vasomotor symptoms)

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

End point timeframe:

Week 0 (Baseline), Week 4.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[2] - ITT

[3] - ITT

[4] - ITT

Statistical analyses

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

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

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

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

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

End point description:

Efficacy Study Part

The weekly frequency of moderate to severe VMS at baseline is defined as the sum of all recorded moderate to severe VMS experienced during the last 7 consecutive days prior randomization.

The weekly frequency of moderate to severe VMS at Week 12 is defined as the sum of all recorded moderate to severe VMS experienced during Week 12.

(VMS=vasomotor symptoms)

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

End point timeframe:

Week 0 (Baseline), Week 12.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[6] - ITT

[7] - ITT

[8] - ITT

Statistical analyses

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

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

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

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

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

End point description:

Efficacy Study Part

The mean severity score of VMS at Baseline is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during the last 7 days prior randomization.

The mean severity score of VMS at Week 4 is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during Week 4.

(VMS=vasomotor symptoms)

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

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

Results are shown as change in mean severity score.

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

End point timeframe:

Week 0 (Baseline) and Week 4.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[10] - ITT

[11] - ITT

[12] - ITT

Statistical analyses

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

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

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

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

End point description:

Efficacy Study Part

The mean severity score of VMS at Baseline is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during the last 7 days prior randomization.

The mean severity score of VMS at Week 12 is defined as the arithmetic mean of the daily severity score values of moderate and severe VMS experienced during Week 12.

(VMS=vasomotor symptoms)

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

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

Results are shown as change in mean severity score.

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

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[14] - ITT

[15] - ITT

[16] - ITT

Statistical analyses

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

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

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

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

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

End point description:

Safety Study Part

A summary of the Final/Consensus diagnosis of endometrial biopsies across all post-baseline visits is provided.

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

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

End point timeframe:

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

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Safety Study Part is single arm.

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

Justification: This endpoint belongs to the Safety Study Part, which is single arm (Arm 4).

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Safety Study Part

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

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

End point timeframe:

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

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Safety Study Part is single arm.

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

Justification: This endpoint belongs to the Safety Study Part, which is single arm (Arm 4).

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Efficacy Study Part

The percentage of subjects with $\geq 50\%$ and $\geq 75\%$ reduction in frequency of moderate to severe VMS from Baseline is presented for each treatment group.

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

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[24] - ITT

[25] - ITT

[26] - ITT

Statistical analyses

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

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

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

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

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

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

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

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

End point description:

Efficacy Study Part

Percentage of subjects with a CID compared to Baseline in the weekly frequency of moderate to severe VMS at Week 4 using the Clinical Global Impression (CGI) questionnaire.

CGI questionnaire: questionnaire in which subjects were to answer the question "Rate the total improvement, whether or not in your judgement it is due entirely to drug treatment. Compared to your condition at administration to the study, how much has it changed?". The options were: very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse.

CID (=Clinically Important Difference) = much improved + very much improved;

MCID (=Minimally Clinically Important Difference) = minimally improved.

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

End point timeframe:

Week 4

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[28] - ITT

[29] - ITT

[30] - ITT

Statistical analyses

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

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

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

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

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

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

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

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

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

End point description:

Efficacy Study Part

Percentage of subjects with a CID compared to Baseline in the weekly frequency of moderate to severe VMS at Week 12 using the Clinical Global Impression (CGI) questionnaire.

CGI questionnaire, CID, MCID: see description above.

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

End point timeframe:

Week 12.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[32] - ITT

[33] - ITT

[34] - ITT

Statistical analyses

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

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

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

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

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

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

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

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

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

assessment) using VVA questionnaire -- Efficacy Study Part

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

End point description:

Efficacy Study Part

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

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

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

Dyspareunia=Vaginal Pain Associated with Sexual Activity

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

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[36] - ITT

N=162 for Vaginal and/or Vulvar Irritation/Itching

[37] - ITT

N=159 Vaginal and/or Vulvar Irritation/Itching

[38] - ITT

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

N=160 Dysuria

Statistical analyses

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

Statistical analysis description:

Model-Adjusted Change from Baseline vs. Placebo

| | |
|-------------------|--------------------|
| Comparison groups | E4 15 mg v Placebo |
|-------------------|--------------------|

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

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

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

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

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

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

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

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

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

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

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

End point description:

Efficacy Study Part

Change from Baseline to Week 12 in HRQoL using the MENQOL questionnaire.

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

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

End point timeframe:

Week 0 (Baseline) and Week 12.

Notes:

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

Justification: This endpoint belongs to the Efficacy Study Part and statistics are presented for all arms of the Efficacy Study Part, i.e., Arms 1-3.

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

Notes:

[40] - ITT

[41] - ITT

N=160 for Vasomotor Domain Score

[42] - ITT

Statistical analyses

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

Statistical analysis description:

Model-Adjusted Change from Baseline vs. Placebo

| | |
|-------------------|--------------------|
| Comparison groups | E4 15 mg v Placebo |
|-------------------|--------------------|

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

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

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

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

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

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

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

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

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

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

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

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

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

End point description:

Efficacy Study Part

A summary of the Final/Consensus diagnosis of endometrial biopsies across all post-baseline visits is provided.

An endometrial biopsy was obtained during the Screening period and at the EOT/Early Discontinuation visit. An additional unscheduled biopsy could have been taken if a subject presented with endometrial thickness >10 mm on TVUS, or persistent and/or recurrent bleeding. Biopsies were read by a panel of 3

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

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

End point timeframe:

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

Notes:

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

Justification: Secondary study endpoint; no statistics presented.

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

Notes:

[44] - SAF

N=74 with performed post-baseline biopsy

N=67 with evaluable post-baseline biopsy

[45] - SAF

N=66 with performed post-baseline biopsy

N=62 with evaluable post-baseline biopsy

[46] - SAF

N=67 with performed post-baseline biopsy

N=56 with evaluable post-baseline biopsy

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Efficacy Study Part

The percentage (95% CI) of subjects in the different endometrial categories is presented. The denominator for the computation of percentages and 95% CIs is the number of subjects with an evaluable post-baseline biopsy in the SAF.

For details, refer to the description text of the previous endpoint.

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

End point timeframe:

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

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Efficacy Study Part

Frequency (percentage) of women with vaginal bleeding and/or spotting during each 28-day cycle of treatment with E4 based on data in the patient diary.

The number of non-hysterectomized subjects with available bleeding information in diaries during the cycle is shown for each cycle under the results table.

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

End point timeframe:

Cycle 1 to Cycle 4.

Notes:

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

Justification: Secondary study endpoint; no statistics presented.

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

Notes:

[51] - SAF

Cycle 1: N=95

Cycle 2: N=91

Cycle 3: N=83

Cycle 4: N=61

[52] - SAF

Cycle 1: N=96

Cycle 2: N=89

Cycle 3: N=83

Cycle 4: N=49

[53] - SAF

Cycle 1: N=97

Cycle 2: N=93

Cycle 3: N=88

Cycle 4: N=62

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Efficacy Study Part

Number of days with bleeding and/or spotting during each 28-day cycle of treatment based on data in the patient diary.

The number of non-hysterectomized subjects with vaginal bleeding and/or spotting is shown for each cycle under the results table.

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

End point timeframe:

Cycle 1 to Cycle 4.

Notes:

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

Justification: Secondary study endpoint; no statistics presented.

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

Notes:

[55] - SAF

Cycle 1: N=10

Cycle 2: N=36

Cycle 3: N=55

Cycle 4: N=21

[56] - SAF

Cycle 1: N=9

Cycle 2: N=36

Cycle 3: N=56

Cycle 4: N=20

[57] - SAF

Cycle 1: N=6

Cycle 2: N=1

Cycle 3: N=4

Cycle 4: N=3

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | 16_Number of subjects with serious adverse events by Hysterectomy Status (Hysterectomized and Non-Hysterectomized) -- Efficacy Study Part |
| End point description: Efficacy Study Part Number of subjects with serious treatment emergent adverse events belonging to the system organ class (SOC) Reproductive system and breast disorders by hysterectomy status (hysterectomized and non-hysterectomized). | |
| End point type | Secondary |
| End point timeframe: From Day 1 (first IMP intake) until Week 13 (hysterectomized subjects) or Week 15/16 (non-hysterectomized subjects). | |

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

Notes:

[58] - SAF

[59] - SAF

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

[60] - SAF

[61] - SAF

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

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

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

Notes:

[62] - SAF

[63] - SAF

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Efficacy Study Part

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

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

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

End point timeframe:

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

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

Notes:

[64] - SAF

[65] - SAF

[66] - SAF

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Efficacy Study Part

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

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

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

End point timeframe:

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

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

Notes:

[67] - SAF

[68] - SAF

[69] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (first IMP intake) until:

Week 13 for Efficacy Study Part: Hysterectomized participants

Week 15/16 for Efficacy Study Part: Non Hysterectomized participants

Week 55/56 for Safety Study Part: All participants

Adverse event reporting additional description:

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

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

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

Reporting groups

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None.

Notes: