



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Multicenter, Proof-of-concept Study to Evaluate a Combined Oral Contraceptive (COC) Containing 30 µg Ethinylestradiol and 150 µg Levonorgestrel Plus 50 mg Dehydroepiandrosterone (DHEA) or Placebo to Counteract Distressing Decreased Sexual Desire Secondary to COC Use

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-000716-30 |
| Trial protocol | HU BG PL CZ RO |
| Global end of trial date | 10 July 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 25 July 2024 |
| First version publication date | 25 July 2024 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | RGL-003-001 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gedeon Richter Plc |
| Sponsor organisation address | Gyömrői út 19-21, Budapest, Hungary, 1103 |
| Public contact | Medical Information Scientific Services, Gedeon Richter Plc., +36 1505 7032, medinfo@richter.hu |
| Scientific contact | Balazs Lazar, Gedeon Richter Plc., +36 20 416 2804, RA.ctaRichter@richter.hu |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 July 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 July 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of DHEA (50 mg daily dose) relative to placebo in women with COC-associated distressing loss of sexual desire (Hypoactive Sexual Desire Disorder (HSDD) secondary to COC use) as measured by Profile of Female Sexual Function (PFSF) Desire domain.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH) guidelines, and local legal requirements. It complies with the ethical principles described in the 18th World Medical Assembly declaration (Declaration of Helsinki, 1964) and amendments of the 29th (Tokyo 1975), 35th (Venice 1983), 41st (Hong Kong 1989) and 48th (South Africa 1996) World Medical Assemblies, to the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 02 November 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Poland: 277 |
| Country: Number of subjects enrolled | Romania: 46 |
| Country: Number of subjects enrolled | Bulgaria: 27 |
| Country: Number of subjects enrolled | Czechia: 22 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Worldwide total number of subjects | 397 |
| EEA total number of subjects | 397 |

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) | 397 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 51 sites in Europe and consisted of a 9-week pretreatment period, a 12-week open-label treatment period (Treatment Period 1), a second 12-week double-blind treatment period (Treatment Period 2), and a 1-week follow-up period.

Pre-assignment

Screening details:

A total of 662 participants were screened of whom 397 enrolled and were treated in Treatment Period 1. A total of 168 qualifying participants continued to Treatment Period 2 and were randomized to double-blind DHEA 50 mg or placebo in a 1:1 ratio.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Treatment Period 1 |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------------------------------|
| Arm title | Combined oral contraceptives (COC) |
|-----------|------------------------------------|

Arm description:

One COC tablet containing 30 µg ethinylestradiol (EE) and 150 µg levonorgestrel (LNG) was taken orally, once daily, for 21 consecutive days, followed by a 7-day tablet-free interval from Day 22 to Day 28 of each cycle. This 28-day cyclic regimen was taken for 3 cycles in Treatment Period 1.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | COC tablet |
| Investigational medicinal product code | |
| Other name | (Oestrogen) Ethinylestradiol and (Progestogen) Levonorgestrel |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Taken once daily by mouth, in the morning, and at the same time each day in the order directed on the blister package.

| Number of subjects in period 1 | Combined oral contraceptives (COC) |
|--------------------------------|------------------------------------|
| Started | 397 |
| Completed | 289 |
| Not completed | 108 |
| Consent withdrawn by subject | 36 |
| Physician decision | 7 |
| Adverse event, non-fatal | 19 |
| Not specified | 42 |
| Lost to follow-up | 4 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | Treatment Period 2 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | DHEA 50 mg + COC |

Arm description:

Eligible participants who completed Treatment Period 1 and qualified at the second baseline (Visit 8) continued to receive COC treatment and were randomized to also receive DHEA during Treatment Period 2. In the second treatment period, one COC tablet containing 30 µg EE and 150 µg LNG was taken on Days 1 to 21, and two 25 mg DHEA tablets were taken on Days 1 to 28 of each 28-day cycle. COC + DHEA were taken together, once daily, in the morning, and with a meal. This 28-day cyclic regimen was to be taken for 3 consecutive cycles.

| | |
|--|-------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Prasterone |
| Investigational medicinal product code | |
| Other name | Dehydroepiandrosterone (DHEA) |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet of combined 30 µg EE/150 µg LNG and two 25 mg DHEA/placebo tablets were to be taken together once daily, in the morning, with a meal.

| | |
|--|---|
| Investigational medicinal product name | COC tablet |
| Investigational medicinal product code | |
| Other name | (Oestrogen) Ethinylestradiol and (Progestogen) Levonorgestrel |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Taken once daily by mouth, in the morning, and at the same time each day in the order directed on the blister package.

| | |
|------------------|---------------|
| Arm title | Placebo + COC |
|------------------|---------------|

Arm description:

Eligible participants who completed Treatment Period 1 and qualified at the second baseline (Visit 8) continued to receive COC treatment and were randomized to also receive placebo during Treatment Period 2. One COC tablet containing 30 µg EE and 150 µg LNG was taken on Days 1 to 21 of each cycle and two matching placebo (DHEA) tablets were taken on Days 1 to 28 of each 28-day cycle. COC + placebo were taken together, once daily, in the morning, and with a meal. This 28-day cyclic regimen was to be taken for 3 consecutive cycles.

One participant who was randomised to the placebo + COC arm but was never dosed with the blinded treatment, leading to the exclusion from the Full Analysis Set (FAS) population.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | COC tablet |
| Investigational medicinal product code | |
| Other name | (Oestrogen) Ethinylestradiol and (Progestogen) Levonorgestrel |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Taken once daily by mouth, in the morning, and at the same time each day in the order directed on the blister package.

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

Dosage and administration details:

Two matching placebo (DHEA) tablets were taken on Days 1 to 28 of each cycle.

| Number of subjects in period 2^[1] | DHEA 50 mg + COC | Placebo + COC |
|---|------------------|---------------|
| | | |
| Started | 84 | 84 |
| Completed | 68 | 67 |
| Not completed | 16 | 17 |
| Consent withdrawn by subject | 7 | 8 |
| Physician decision | - | 1 |
| Failure to meet Continuation criteria | - | 1 |
| Adverse event, non-fatal | 3 | 3 |
| Not specified | 3 | 2 |
| Lost to follow-up | 2 | 1 |
| Lack of efficacy | 1 | - |
| Not treated | - | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 289 participants that completed Treatment Period 1, 168 of those participants qualified and were randomized in Treatment Period 2.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Treatment Period 1 |
|-----------------------|--------------------|

Reporting group description:

One COC tablet containing 30 µg ethinylestradiol (EE) and 150 µg levonorgestrel (LNG) was taken orally, once daily, for 21 consecutive days, followed by a 7-day tablet-free interval from Day 22 to Day 28 of each cycle. This 28-day cyclic regimen was taken for 3 cycles in Treatment Period 1.

| Reporting group values | Treatment Period 1 | Total | |
|---|--------------------|-------|--|
| Number of subjects | 397 | 397 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 397 | 397 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 29.0 | | |
| standard deviation | ± 6.75 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 397 | 397 | |
| Male | 0 | 0 | |
| Race | | | |
| Units: Subjects | | | |
| Black or African American | 1 | 1 | |
| White | 287 | 287 | |
| Other | 109 | 109 | |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Combined oral contraceptives (COC) |
| Reporting group description: One COC tablet containing 30 µg ethinylestradiol (EE) and 150 µg levonorgestrel (LNG) was taken orally, once daily, for 21 consecutive days, followed by a 7-day tablet-free interval from Day 22 to Day 28 of each cycle. This 28-day cyclic regimen was taken for 3 cycles in Treatment Period 1. | |
| Reporting group title | DHEA 50 mg + COC |
| Reporting group description: Eligible participants who completed Treatment Period 1 and qualified at the second baseline (Visit 8) continued to receive COC treatment and were randomized to also receive DHEA during Treatment Period 2. In the second treatment period, one COC tablet containing 30 µg EE and 150 µg LNG was taken on Days 1 to 21, and two 25 mg DHEA tablets were taken on Days 1 to 28 of each 28-day cycle. COC + DHEA were taken together, once daily, in the morning, and with a meal. This 28-day cyclic regimen was to be taken for 3 consecutive cycles. | |
| Reporting group title | Placebo + COC |
| Reporting group description: Eligible participants who completed Treatment Period 1 and qualified at the second baseline (Visit 8) continued to receive COC treatment and were randomized to also receive placebo during Treatment Period 2. One COC tablet containing 30 µg EE and 150 µg LNG was taken on Days 1 to 21 of each cycle and two matching placebo (DHEA) tablets were taken on Days 1 to 28 of each 28-day cycle. COC + placebo were taken together, once daily, in the morning, and with a meal. This 28-day cyclic regimen was to be taken for 3 consecutive cycles. One participant who was randomised to the placebo + COC arm but was never dosed with the blinded treatment, leading to the exclusion from the Full Analysis Set (FAS) population. | |

Primary: Change from Baseline in PFSF Desire Domain at Day 168

| | |
|--|---|
| End point title | Change from Baseline in PFSF Desire Domain at Day 168 |
| End point description: The Profile of Female Sexual Function (PFSF) is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Desire Domain consisting of 9 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Desire domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function. FAS: All participants who were randomized to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received. | |
| End point type | Primary |
| End point timeframe: Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 25.470 (± 20.7323) | 31.371 (± 20.9626) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change from Baseline in PFSF Desire Domain Score |
| Statistical analysis description: Change from Baseline in PFSF Desire Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0538 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.725 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.561 |
| upper limit | 0.112 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.473 |

Secondary: Change from Baseline in Female Sexual Distress Scale-Revised (FSDS-R) Item 13 Score at Day 168

| | |
|--|--|
| End point title | Change from Baseline in Female Sexual Distress Scale-Revised (FSDS-R) Item 13 Score at Day 168 |
| End point description: The FSDS-R is a questionnaire completed by the participants themselves which assesses distress related to sexuality over the past 30 days. FSDS-R has 13 items, each scored on a 5-point scale, where 0 = "Never" and 4 = "Always", with higher scores indicating more sexually related distress. Item 13 specifically asks to what degree participants felt "Bothered by Low Sexual Desire" over the past 30 days. FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analysed according to their randomised treatment regardless of the actual treatment received. | |
| End point type | Secondary |
| End point timeframe: Baseline and Day 168 | |

| | | | | |
|--|--------------------|--------------------|--|--|
| End point values | DHEA 50 mg + COC | Placebo + COC | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168; n=80,n=79 | -1.4 (\pm 1.40) | -1.3 (\pm 1.31) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change from Baseline in FSDS-R Item 13 Score |
| Statistical analysis description: Change from Baseline in FSDS-R Item 13 Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8972 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.024 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.348 |
| upper limit | 0.397 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.189 |

Secondary: Number of Subjects Answering the Subject's Meaningful Benefit Question with Yes at Day 168

| | |
|--|--|
| End point title | Number of Subjects Answering the Subject's Meaningful Benefit Question with Yes at Day 168 |
| End point description: Subject's Meaningful Benefit Question was: "Overall, do you believe you have experienced a meaningful benefit from the study medication?", to be answered with "Yes/No". The data were collected per electronic patient-reported outcomes. FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analysed according to their randomised treatment, regardless of the actual treatment received. | |
| End point type | Secondary |
| End point timeframe: Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Count of Subjects | | | | |
| Responder n=79, n=79 | 47 | 45 | | |
| Non-responder n=79, n=79 | 32 | 34 | | |

Statistical analyses

| Statistical analysis title | Answering the Patient's Meaningful Question Yes |
|--|---|
| Statistical analysis description: | |
| Analysis Number of Subjects Answering the Patient's Meaningful Benefit Question as Yes at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.747 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 2.089 |

Secondary: Change from Baseline in PFSF Responsiveness Domain at Day 168

| End point title | Change from Baseline in PFSF Responsiveness Domain at Day 168 |
|--|---|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Responsiveness Domain consisting of 7 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Responsiveness domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 24.526 (\pm 20.3094) | 28.619 (\pm 17.2985) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Responsiveness Domain |
|--|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Responsiveness Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4531 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.031 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.368 |
| upper limit | 3.307 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.699 |

Secondary: Change from Baseline in PFSF Arousal Domain at Day 168

| End point title | Change from Baseline in PFSF Arousal Domain at Day 168 |
|--|--|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Arousal domain consisting of 3 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Arousal domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 34.359 (\pm 29.2787) | 35.889 (\pm 27.8025) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Arousal Domain Score |
|---|---|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Arousal Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6865 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.763 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.354 |
| upper limit | 6.827 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.364 |

Secondary: Change from Baseline in PFSF Orgasm Domain at Day 168

| End point title | Change from Baseline in PFSF Orgasm Domain at Day 168 |
|---|---|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Orgasm Domain consisting of 4 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Orgasm domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: All participants who were randomized to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 34.0 (± 26.22) | 32.3 (± 24.29) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Orgasm Domain Score |
|--|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Orgasm Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8709 |
| Method | mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.634 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.067 |
| upper limit | 8.335 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.895 |

Secondary: Change from Baseline in PFSF Pleasure Domain at Day 168

| End point title | Change from Baseline in PFSF Pleasure Domain at Day 168 |
|---|---|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Pleasure Domain consisting of 7 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Pleasure domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: All participants who were randomized to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 31.341 (\pm 26.5778) | 32.953 (\pm 23.4871) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Pleasure Domain Score |
|--|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Pleasure Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4721 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.968 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.082 |
| upper limit | 5.146 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.121 |

Secondary: Change from Baseline in PFSF Concerns Domain at Day 168

| End point title | Change from Baseline in PFSF Concerns Domain at Day 168 |
|---|---|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Concerns Domain consisting of 3 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Concerns domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: All participants who were randomized to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 28.615 (\pm 26.5289) | 33.778 (\pm 25.4484) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Concerns Domain Score |
|--|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Concerns Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | Placebo + COC v DHEA 50 mg + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3137 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.918 |
| upper limit | 3.84 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.001 |

Secondary: Change from Baseline in PFSF Self-image Domain at Day 168

| End point title | Change from Baseline in PFSF Self-image Domain at Day 168 |
|---|---|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF has 7 domains one of which is the PFSF Self-image Domain consisting of 4 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never". These item scores were then summed into a PFSF Self-image domain score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: All participants who were randomized to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analyzed according to their randomized treatment regardless of the actual treatment received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 168 | |

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=65,n=60 | 28.6 (± 24.88) | 34.4 (± 20.79) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Self-Image Domain |
|--|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Self-Image Domain Score at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2115 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.713 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.121 |
| upper limit | 2.695 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.763 |

Secondary: Change from Baseline in PFSF Total Score at Day 168

| End point title | Change from Baseline in PFSF Total Score at Day 168 |
|--|---|
| End point description: | |
| <p>The PFSF is a questionnaire completed by the participant themselves which assesses the participant's sexual function over the past 4 weeks. The PFSF consists of 37 questionnaire items with each item scored from 1 to 6 on a 6-point scale where 1 = "Always" and 6 = "Never" and an additional global „Satisfaction with Sexuality" item which is scored from 1 to 5 on a 5-point scale where 1 = "Poor" and 5 = "Excellent". These item scores were then summed into a PFSF Total score which was transformed to a 0-100 point scale where higher scores indicated a more favourable sexual function.</p> <p>FAS: All participants who were randomized to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analysed according to their randomised treatment, regardless of the actual treatment received.</p> | |
| End point type | Secondary |

End point timeframe:

Baseline and Day 168

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|--|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168; n=65,n=60 | 28.641 (\pm 20.7389) | 32.145 (\pm 18.5014) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PFSF Total Score |
|--|--|
| Statistical analysis description: | |
| Analysis of Change from Baseline in PFSF Total Score at Day 168 of treatment period 2. | |
| Comparison groups | Placebo + COC v DHEA 50 mg + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2571 |
| Method | Mixed effect repeated measures |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.769 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.305 |
| upper limit | 2.766 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.319 |

Secondary: Change from Baseline in Patient's Global Impression of Change (PGIC) at Day 168

| | |
|---|---|
| End point title | Change from Baseline in Patient's Global Impression of Change (PGIC) at Day 168 |
| End point description: | |
| <p>The PGIC is a 1-item question that assessed change in a participant's sexual desire (and feeling bothered about a lack of it) since the start of the current study treatment. Participants rated the change on a 6-point scale. Participants rated this change as very much improved, much improved, moderately improved, minimally improved, no change and worse, where 1= "Very much improved" to 6 = "Worse". FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analysed according to their randomised treatment, regardless of the actual treatment received.</p> | |
| End point type | Secondary |

End point timeframe:

Baseline and Day 168

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|---|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 14 (CYCLE 6 DAY 28/EOT) - Day 168;n=79,n=79 | -2.3 (± 1.62) | -2.3 (± 1.69) | | |

Statistical analyses

| Statistical analysis title | Change from Baseline in PGIC |
|---|----------------------------------|
| Statistical analysis description: | |
| Analysis of Change from Baseline in Patient's Global Impression of Change at Day 168 of treatment period 2. | |
| Comparison groups | DHEA 50 mg + COC v Placebo + COC |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.935 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.021 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.538 |
| upper limit | 0.495 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.262 |

Secondary: Change from Baseline Values of Endocrine Parameters by Visit at Treatment Period 1

| | |
|-----------------|--|
| End point title | Change from Baseline Values of Endocrine Parameters by Visit at Treatment Period 1 |
|-----------------|--|

End point description:

All endocrine blood samples were taken between 7 AM and 9 AM. Endocrine measurements included 17-beta-Estradiol (unit: pg/ml), testosterone free serum (unit: pg/ml), testosterone total serum (unit: µg/l), sex hormone binding globulin (SHBG) (unit: nmol/l), Dehydroepiandrosterone, Prasterone (DHEA) serum (unit: µg/l), Dehydroepiandrosterone sulfate (DHEAS) serum (unit: ng/ml), dihydrotestosterone (unit: ng/l), 3 alpha-androstanediol Glucuronide (3α- ADG) (unit: ng/mL), Androstenedione serum (unit: µg/l), and estrone serum (unit: pg/ml). At the Enrolment visit it was recommended to take endocrine samples after eligibility had been confirmed and participant had been enrolled to the study.

FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took

at least 1 dose of blinded study treatment. Participants were analysed according to their randomised treatment, regardless of the actual treatment received.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Visit 4 (Cycle 1 Day 15± 3) to Visit 7 (Cycle 3 Day 15 ± 3) | |

| End point values | Combined oral contraceptives (COC) | | | |
|---|------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 167 | | | |
| Units: Concentration | | | | |
| arithmetic mean (standard deviation) | | | | |
| 17-beta-Estradiol Visit 4, n=153 | -114.23 (± 128.730) | | | |
| 17-beta-Estradiol Visit 7, n=142 | -106.66 (± 121.292) | | | |
| 3α- ADG Visit 4, n=152 | -0.64 (± 5.815) | | | |
| 3α- ADG Visit 7, n=141 | -0.23 (± 10.649) | | | |
| Androstenedione serum Visit 4, n=153 | -0.651 (± 0.5441) | | | |
| Androstenedione serum Visit 7, n=141 | -0.572 (± 0.5459) | | | |
| DHEA serum Visit 4, n=153 | -1.48 (± 3.117) | | | |
| DHEA serum Visit 7, n= 141 | -1.42 (± 2.895) | | | |
| DHEAS serum Visit 4, n=153 | -263.1 (± 733.71) | | | |
| DHEAS serum Visit 7, n=142 | -355.5 (± 768.37) | | | |
| Dihydrotestosterone Visit 4, n=155 | -31.1 (± 40.39) | | | |
| Dihydrotestosterone Visit 7, n=144 | -33.2 (± 39.22) | | | |
| Estrone serum Visit 4, n=154 | -60.06 (± 79.029) | | | |
| Estrone serum Visit 7, n=145 | -48.88 (± 55.567) | | | |
| SHBG serum Visit 4, n=154 | 26.35 (± 28.050) | | | |
| SHBG serum Visit 7, n=144 | 31.68 (± 33.473) | | | |
| Testosterone free serum Visit 4, n=155 | -0.429 (± 0.6104) | | | |
| Testosterone free serum Visit 7, n=145 | -0.370 (± 0.5588) | | | |
| Testosterone total serum Visit 4, n=153 | -0.138 (± 0.1355) | | | |
| Testosterone total serum Visit 7, n=141 | -0.116 (± 0.1349) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Values of Endocrine Parameters by Visit at Treatment Period 2

| | |
|-----------------|--|
| End point title | Change from Baseline Values of Endocrine Parameters by Visit at Treatment Period 2 |
|-----------------|--|

End point description:

All endocrine blood samples were taken between 7 AM and 9 AM. Endocrine measurements included 17-beta-Estradiol (unit: pg/ml), testosterone free serum (unit: pg/ml), testosterone total serum (unit: µg/l), SHBG serum (unit: nmol/l), DHEA serum (unit: µg/l), DHEAS serum (unit: ng/ml), dihydrotestosterone (unit: ng/l), 3α-ADG (unit: ng/mL), Androstenedione serum (unit: µg/l), and estrone serum (unit: pg/ml). At the Enrolment visit it was recommended to take endocrine samples after eligibility had been confirmed and participant had been enrolled to the study.

FAS: Consisted of all participants who were randomised to one of the blinded treatment arms and took at least 1 dose of blinded study treatment. Participants were analysed according to their randomised treatment, regardless of the actual treatment received.

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

End point timeframe:

Baseline and Visit 9 (Cycle 4 Day 15± 3) to Visit 13 (Cycle 6 Day 15± 3)

| End point values | DHEA 50 mg + COC | Placebo + COC | | |
|--|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 83 | | |
| Units: Concentration | | | | |
| arithmetic mean (standard deviation) | | | | |
| Androstenedione serum Visit 9, (n=55, 50) | 0.379 (± 0.7817) | -0.047 (± 0.5679) | | |
| Androstenedione serum Visit 11, (n=54, 40) | 0.280 (± 0.7869) | -0.008 (± 0.5066) | | |
| Androstenedione serum Visit 13, (n=55, 38) | 0.392 (± 0.6414) | -0.033 (± 0.4982) | | |
| DHEA serum Visit 9, (n=55, 50) | 0.25 (± 4.004) | -0.02 (± 2.576) | | |
| DHEA serum Visit 11, (n=54, 40) | 0.32 (± 3.778) | 0.25 (± 2.968) | | |
| DHEA serum Visit 13, (n=55, 38) | 1.46 (± 2.664) | -0.12 (± 2.754) | | |
| Dihydrotestosterone Visit 9, (n=61, 54) | 31.0 (± 56.60) | -5.6 (± 30.27) | | |
| Dihydrotestosterone Visit 11, (n=54, 41) | 31.0 (± 61.94) | -2.8 (± 18.32) | | |
| Dihydrotestosterone Visit 13, (n=55, 40) | 31.7 (± 46.20) | -3.1 (± 25.69) | | |
| Estrone serum Visit 9, (n=61, 55) | 6.23 (± 42.610) | -10.04 (± 58.347) | | |

| | | | | |
|---|--------------------|-------------------|--|--|
| Estrone serum Visit 11, (n=54, 43) | 9.78 (± 46.593) | 3.96 (± 100.192) | | |
| Estrone serum Visit 13, (n=55, 41) | 6.80 (± 45.147) | -2.66 (± 60.739) | | |
| SHBG serum Visit 9, (n=60, 55) | 7.58 (± 29.650) | -0.43 (± 28.099) | | |
| SHBG serum Visit 11, (n=54, 43) | -1.18 (± 16.125) | -7.09 (± 30.707) | | |
| SHBG serum Visit 13, (n=54, 41) | -0.29 (± 31.614) | -9.39 (± 20.162) | | |
| Testosterone free serum Visit 9, (n=61, 55) | 0.160 (± 0.7942) | -0.041 (± 0.4559) | | |
| Testosterone free serum Visit 11, (n=54, 43) | 0.237 (± 0.6697) | 0.017 (± 0.5846) | | |
| Testosterone free serum Visit 13, (n=55, 41) | 0.130 (± 0.4919) | -0.140 (± 0.5037) | | |
| Testosterone total serum Visit 9, (n=55, 50) | 0.114 (± 0.1705) | -0.030 (± 0.1150) | | |
| Testosterone total serum Visit 11, (n=54, 40) | 0.110 (± 0.2093) | -0.009 (± 0.1080) | | |
| Testosterone total serum Visit 13, (n=55, 38) | 0.118 (± 0.1610) | -0.024 (± 0.1181) | | |
| DHEAS serum Visit 9, (n=60, 54) | 1661.4 (± 2743.41) | 5.3 (± 1025.31) | | |
| DHEAS serum Visit 11, (n=54, 43) | 1720.7 (± 2507.76) | 24.2 (± 696.23) | | |
| DHEAS serum Visit 13, (n=54, 40) | 1723.5 (± 2248.14) | 60.7 (± 719.02) | | |
| 3a- ADG Visit 9, (n=60, 53) | 3.93 (± 5.582) | 0.38 (± 1.753) | | |
| 3a- ADG Visit 11, (n=53, 42) | 7.39 (± 25.141) | -0.57 (± 5.291) | | |
| 3a- ADG Visit 13, (n=53, 39) | 5.30 (± 14.277) | -0.87 (± 6.783) | | |
| 17-beta-Estradiol Visit 9, (n=59, 54) | 2.04 (± 61.807) | -12.46 (± 73.578) | | |
| 17-beta-Estradiol Visit 11, (n=54, 42) | 2.91 (± 49.687) | -5.70 (± 93.648) | | |
| 17-beta-Estradiol Visit 13, (n=55, 39) | 6.12 (± 78.190) | -17.68 (± 80.953) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All non-serious adverse events were reported from signing the informed consent (ICF) through 7-day follow-up period. Serious adverse events were collected from signing of ICF until 30 days after last administration of study drug.

Adverse event reporting additional description:

Safety Set: Safety set consisted of all participants who were administered at least 1 dose of COC or blinded treatment. Participants were analyzed according to the treatment they received.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Combined Oral Contraceptive (COC) |
|-----------------------|-----------------------------------|

Reporting group description:

One COC tablet containing 30 µg ethinylestradiol (EE) and 150 µg levonorgestrel (LNG) was taken orally, once daily, for 21 consecutive days, followed by a 7-day tablet-free interval from Day 22 to Day 28 of each cycle. This 28-day cyclic regimen was taken for 3 cycles in Treatment Period 1.

| | |
|-----------------------|------------------|
| Reporting group title | DHEA 50 mg + COC |
|-----------------------|------------------|

Reporting group description:

Eligible participants who completed Treatment Period 1 and qualified at the second baseline (Visit 8) continued to receive COC treatment and were randomized to also receive DHEA during Treatment Period 2. In the second treatment period, one COC tablet containing 30 µg EE and 150 µg LNG was taken on Days 1 to 21 of each cycle and two 25 mg DHEA tablets were taken on Days 1 to 28 of each 28-day cycle. COC + DHEA were taken together, once daily, in the morning, and with a meal. This 28-day cyclic regimen was to be taken for 3 consecutive cycles.

| | |
|-----------------------|---------------|
| Reporting group title | Placebo + COC |
|-----------------------|---------------|

Reporting group description:

Eligible participants who completed Treatment Period 1 and qualified at the second baseline (Visit 8) continued to receive COC treatment and were randomized to also receive placebo during Treatment Period 2. In the second treatment period, one COC tablet containing 30 µg EE and 150 µg LNG was taken on Days 1 to 21 of each cycle and two matching placebo (DHEA) tablets were taken on Days 1 to 28 of each 28-day cycle. COC + placebo were taken together, once daily, in the morning, and with a meal. This 28-day cyclic regimen was to be taken for 3 consecutive cycles.

| Serious adverse events | Combined Oral Contraceptive (COC) | DHEA 50 mg + COC | Placebo + COC |
|---|-----------------------------------|------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 397 (0.76%) | 0 / 84 (0.00%) | 0 / 84 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | 0 / 84 (0.00%) | 0 / 84 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | 0 / 84 (0.00%) | 0 / 84 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 397 (0.25%) | 0 / 84 (0.00%) | 0 / 84 (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 |

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

| Non-serious adverse events | Combined Oral Contraceptive (COC) | DHEA 50 mg + COC | Placebo + COC |
|---|-----------------------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 87 / 397 (21.91%) | 17 / 84 (20.24%) | 19 / 84 (22.62%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 40 / 397 (10.08%) | 3 / 84 (3.57%) | 8 / 84 (9.52%) |
| occurrences (all) | 50 | 5 | 10 |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 8 / 397 (2.02%) | 8 / 84 (9.52%) | 6 / 84 (7.14%) |
| occurrences (all) | 8 | 9 | 7 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 22 / 397 (5.54%) | 0 / 84 (0.00%) | 0 / 84 (0.00%) |
| occurrences (all) | 31 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 17 / 397 (4.28%) | 6 / 84 (7.14%) | 5 / 84 (5.95%) |
| occurrences (all) | 18 | 6 | 6 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 12 April 2021 | <ul style="list-style-type: none">-It was planned that approximately 55 centres would be initiated for this study in up to 7 countries in geographical Europe.-Planned duration of participant's participation extended up to approximately 34 weeks (including screening and safety follow-up).-Replaced "Exploratory" with "Additional" to harmonise naming of Objective with Additional endpoint.-Resolved discrepancy in listing of objectives and endpoints-Updated exclusion criteria to include the presence of more than one risk factor (for women \leq 35 years of age) or one risk factor (for women $>$ 35 years of age) for vascular disease (eg, dyslipoproteinaemia; smoking; venous or arterial thromboembolism in sibling or parent below the age of 50; controlled arterial hypertension; obesity [BMI over 30 kg/m²]; migraine).-Updated exclusion criteria to include a history during pregnancy or during previous oestrogen use of severe pruritus, herpes gestationis, or deterioration of otosclerosis, chloasma, hereditary or acquired vasomotor oedema.-Updated statistical methods and secondary endpoints from Treatment Period 2 baseline to Day 168 for analysis of the FSDS-R Item 13, using an Analysis of covariance model with Treatment Period 2 baseline values as a covariate and treatment group as factor.-Updated statistical methods and secondary endpoints to the proportion of participants answering the Patient's Meaningful Benefit Question with "yes" was to be analysed by logistic regression using treatment group as factor. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|--|------------------|
| 01 June 2021 | Screening was put on hold globally for the study between 01 June 2021 and re-started on 15 November 2021. Reason: Expiry of old Biosteron (DHEA) and lack of Biosteron availability on the market necessitated putting screening on-hold. | 15 November 2021 |

Notes:

Limitations and caveats

None reported