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
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 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
Physician decision	7
Consent withdrawn by subject	36
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 (± 1.40)	-1.3 (± 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:

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.
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.

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 (± 20.3094)	28.619 (± 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:

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.
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.

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 (± 29.2787)	35.889 (± 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:

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.
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	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:

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.
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	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 (± 26.5778)	32.953 (± 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:

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.
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	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 (± 26.5289)	33.778 (± 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:

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.
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	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:

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.
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.

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 (± 20.7389)	32.145 (± 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:

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.

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)		
3α- ADG Visit 9, (n=60, 53)	3.93 (± 5.582)	0.38 (± 1.753)		
3α- ADG Visit 11, (n=53, 42)	7.39 (± 25.141)	-0.57 (± 5.291)		
3α- 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	-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 ≤ 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/m^2]; 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