Clinical Study Synopsis

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Date of study report:	20 APR 2010
Study title:	Multi-center, double-blind, placebo-controlled study to investigate the efficacy and safety of daily oral 100 mg dehydroepiandrosterone (DHEA) over 6 treatment cycles as a concomitant therapy to oral contraceptives (OC) to alleviate complaints of reduced libido in women with acquired female sexual dysfunction (FSD) associated with OC-use
Sponsor's study number:	91692 (310741)
NCT number:	NCT00566384
EudraCT number:	2006-004397-27
Sponsor:	Bayer HealthCare
Clinical phase:	Phase 2
Study objectives:	Primary objective: To investigate the effects of 100 mg DHEA per day in women on continuous treatment with a monophasic combined oral contraceptive (COC) who suffered from acquired FSD as a perceived adverse drug reaction to their OC use. The primary objective consisted of the combined sexual arousal and desire domains of the Female Sexual Function Index (FSFI) self-report questionnaire. Secondary objectives: Other domains of the FSFI were investigated and other self-report measures were used in order to explore possible specific effects of DHEA. Further study objectives were: • To better define the study population, the endpoints, and the sample size for future Phase 2 and Phase 3 clinical trials. • To better understand hormonal levels in women with sexual dysfunction and their changes under treatment with DHEA. • To investigate the safety of DHEA and to further evaluate its adverse drug reaction profile. • To determine the exposure of DHEA and some important metabolites like dehydroepiandrosterone sulfate (DHEA-S) and testosterone (T) and to investigate their potential impact on the sex hormone-binding globulin (SHBG).
Test drug:	DHEA (SH K04828A; BAY 86-5314)
Name of active ingredient(s):	DHEA
Dose:	100 mg/day
Route of administration:	The study drug (2 capsules each containing 50 mg DHEA) was taken orally, once daily along with the OC pill, preferably always at the same time of the

	day.
Duration of treatment:	The duration of treatment was 168 days (i.e., 6 cycles of 28 days each).
Reference drug:	Matching placebo capsules
Dose:	Not applicable
Route of administration:	Placebo capsules were taken orally, once daily, along with the OC pill, preferably always at the same time of the day.
Duration of treatment:	The duration of treatment was 168 days (i.e., 6 cycles of 28 days each)
Background treatment:	Combined oral contraceptive
Indication:	Acquired OC-associated FSD
Diagnosis and main criteria for inclusion:	• Age between 18 and 35 years (inclusive), smokers maximum age of 30 years (inclusive) at Visit 1 • Women on treatment with a monophasic COC and suffering from reduced libido as a perceived adverse drug reaction of the OC (i.e., acquired OC-associated FSD) for at least 3 months and willing to continue the particular OC that they had been using. • Value of 18 or below in the unweighted sum score of the sexual desire and arousal domain of the FSFI questionnaire at screening and baseline. • Sexual relationship with a sexually competent partner • Non-suspicious cervical smear taken at Visit 1 or within the last 3 months before Visit 1
Study design:	The study was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, two-arm study. The subjects already taking a monophasic COC were randomized in 1:1 ratio to receive in addition to the COC either active study drug or matching placebo.
Methodology:	The study included a screening Visit 1 (6-8 weeks before administration of study medication), an admission Visit 2, 3 treatment visits (after Cycles 2, 4, and 6), and a final Visit 6 (after cycle 6 within 12-19 days after the end of the study medication or in case of premature termination). There was no intake-free interval between consecutive cycles for the study medication. The subjects were asked to record information related to administration of medication in diary cards, and to daily fill the Female Sexual Encounter Profile (FSEP) questionnaire. At each visit, the completed diary cards were collected, reviewed, and signed by the investigator. Blood samples for pharmacokinetic measurements were taken at admission (Visit 2) and Visits 3, 4, 5, and 6. At Visits 3, 4, and 5, two blood samples were collected at an interval of approximately 1 h. In a subgroup of subjects, a more dense blood sampling during one day between Visit 3 and Visit 5 was performed in addition to the other blood samplings. In these subjects, blood was drawn at 30 minutes pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the

	capsule intake. Female sexual function index (FSFI), female sexual distress scale-revised (FSDS-R), psychological general well-being index (PGWBI) self-report questionnaires were filled at each study visit. Vaginal pH was measured at all the study visits. Safety was assessed by recording the baseline findings, concomitant therapy, adverse events (AEs), laboratory evaluations (hematology, serum chemistry), physical examination, gynecological examination, cervical smear, pregnancy test, blood pressure, heart rate, and assessment of the subjects' facial acne. At the final examination (Visit 6), either in case of premature discontinuation or after Cycle 6, the subjects were asked to give a subjective assessment of the treatment in the form of a questionnaire.
Study center(s):	The study was conducted at 11 centers in Germany.
Publication(s) based on the study (references):	None at the time of report creation.
Study period:	Study Start Date: 09 NOV 2007 Study Completion Date: 22 APR 2009
Early termination:	Not applicable
Number of subjects:	Planned: 100 subjects Analyzed: 100 subjects
Criteria for evaluation	
Efficacy:	Efficacy variable (primary) Female Sexual Function Index: The FSFI questionnaire was a 19-item multidimensional self-report questionnaire and was used to assess sexual functioning (sexual desire and arousal component scores) in women in 6 separate dimensions (desire, arousal, lubrication, orgasm, satisfaction, and pain) over the preceding 4 weeks. Change from baseline (Visit 2) to Cycle 6 (Visit 5) in the not-weighted sum of FSFI sexual desire and the sexual arousal component scores, defined as the total of questions 1-6 of the FSFI, was calculated. Efficacy variable (secondary) • The change from baseline to Cycle 6 in the percentage of satisfactory sexual events recorded over a 4 week period. The baseline period is the last 4 weeks between the screening visit and the baseline visit. • The absolute values and change from baseline to Cycle 1 (Visit 3), Cycle 3 (Visit 4), Cycle 6 (Visit 5), and follow-up (Visit 6) in FSFI multidimensional self-report questionnaire (component scores [desire, arousal, lubrication, orgasm, satisfaction, and pain] and total score). • Female Sexual Distress Scale-Revised: The FSDS-R questionnaire is a

validated, 13-item, self-report scale that assesses subjective distress associated with sexual dysfunction in women. The total FSDS-R score was evaluated as the sum of the single items in the questionnaire.

- Female Sexual Encounter Profile: The FSEP is an event log for the description of a sexual encounter including date and time of onset; the activities; and the rating of desire, satisfaction, lubrication, arousal, orgasm, and the successfulness and satisfaction of the encounter. The change from Visit 2 to Visit 5 in the percentage of "successful and satisfactory sexual events" recorded over a 4-week period (one cycle) was evaluated.
- Psychological General Well-Being Index: The PGWBI questionnaire (to measure self-representations of intrapersonal affective or emotional states reflecting a sense of subjective well-being or distress) includes 22 items that, apart from combining into a global overall score, are divided into six dimensions: anxiety, depressed mood, positive well-being, self-control, health, and vitality. The 1-6 point Likert response scale was used in this study. The overall score gives a minimum of 22 and a maximum value of 132. The higher the score, the better the well-being of the subject. The observation phase was the last 4 weeks.
- Patient subjective evaluation (subjective assessment): At the final examination (visit 6), either in case of premature discontinuation or after Cycle 6, the subject was asked to give a subjective assessment using the questions. The investigator asked the patient the questions from subjective evaluation questionnaire and recorded the answers.

Safety: All the AEs were documented and coded by the investigator according to the Medical Dictionary for Regulatory Activities (MedDRA) (last available version before the database lock) and were classified per seriousness, intensity, main pattern, action taken with the study drug, causal relationship to the study drug , causal relationship to the study conduct, and outcome of the event. Other safety variables including, vaginal pH measurements, baseline findings, clinical laboratory parameters (serum chemistry, hematology), physical examination, gynecological examination, cervical smear, pregnancy test, blood pressure and heart rate, facial acne, body weight were evaluated and abnormal findings were noted.

Clinical pharmacology: Pharmacokinetics of DHEA and its major metabolites (DHEA-S as well as testosterone) and SHBG were monitored in all subjects.

Statistical methods: Analysis sets: Full analysis set (FAS) is a set of all randomized subjects with at least one administration of the study medication and with at least one observation after administration of the study medication. Per-protocol set (PPS) is a subset of the FAS and included all subjects except those with major protocol deviations affecting the primary variables. The evaluation of the primary efficacy parameter, test of superiority of DHEA in comparison

	to placebo, was based on the FAS. For the primary target variable, secondary target variables, and selected demographic data, additionally an analysis based on the PPS was done. The analyses of all other target and safety parameters were based on the FAS. Efficacy: The primary efficacy variable, not-weighted sum of sexual desire and arousal component scores (sum of questions 1-6), was evaluated descriptively and was assigned to the non-parametric Wilcoxon Test on a significance level of $\alpha = 0.025$. The results of the FSDS-R questionnaire, FSEP questionnaire, and PGWBI questionnaire were analyzed by descriptive statistics and frequency analysis, as appropriate. A post hoc subpopulation analysis of subjects who had baseline DHEA, DHEA-S, T, and SHBG, hormone levels that were lower than the median of the total group was done. Safety: All safety parameters were subjected to descriptive statistics. The number of data available and missing data, mean, standard deviation (SD), minimum, first quartile, median, third quartile, and maximum were calculated f or metric data. For categorical data, frequency was analyzed. The vaginal pH value was evaluated using descriptive analysis. Clinical pharmacology: For pharmacokinetic analysis, the following statistics were calculated for the serum concentrations of all analytes at each of the sampling points sorted by treatment: arithmetic mean, arithmetic SD, and coefficient of variation (CV), geometric mean, geometric SD (re-transformed SD of the logarithms) and CV; minimum; median; maximum value; and the number of measurements.
Substantial protocol changes:	The study was conducted according to the final study protocol, Version 1.2, from 19 OCT 2007, and included no substantial amendments.

Subject disposition and baseline

The study included 100 subjects in 11 centers taking a monophasic COC and suffering from reduced libido as a perceived adverse drug reaction of the OC (i.e., acquired OC-associated female sexual dysfunction) of at least 3 months duration. They were aged 18-35 years and of normal body mass index (BMI), and were randomized to DHEA or placebo for treatment over 6 menstrual cycles. In FAS, the mean (SD) age was 25.4 (3.5) and 25.8 (4.3) years in DHEA and placebo groups, respectively. In FAS, the mean (SD) BMI was 22.6 (2.9) and 22.8 (2.8) kg/m^2 in DHEA and placebo groups, respectively. All patients were Caucasian, with the exception of one subject in DHEA group.

The study included 51 subjects randomized to DHEA and 49 to placebo. Of the 51 subjects randomized to DHEA treatment, 45 completed treatment. Of the 6 subjects who discontinued prematurely, 3 subjects withdrew consent, 1 subject discontinued due to 2 AEs (nausea and dizziness), 1 subject due to other reasons specified as acne, and one due to other reasons specified as breast tension. Of the 49 subjects randomized to the placebo treatment, 45 subjects completed treatment. Of the 4 subjects who discontinued prematurely, 3 subjects withdrew consent and 1 subject lost to follow-up.

The FAS and safety analysis set included 51 subjects treated with DHEA and 49 with placebo. The PPS included 43 DHEA subjects and 41 placebo subjects. Of the 8 DHEA subjects not in the PPS, 5 were

excluded for major protocol deviations and 3 for other reasons. Of the 8 placebo subjects, 6 were excluded for major protocol deviations and 2 for other reasons. The pharmacokinetic subgroup included 20 subjects, 10 per treatment group. Furthermore, the primary and selected secondary efficacy variables were studied in restricted populations called subpopulations. These subpopulations varied from 27 to 21 per treatment group and were defined by baseline hormone values (median values of FAS).

Efficacy evaluation

Primary efficacy: The primary efficacy variable was the sum of the desire and arousal questions from the FSFI. For FAS, the baseline values were 12.7 (SD 3.90) for the DHEA group and 12.7 (3.80) for the placebo group, maximum for both groups 18, being well below the inclusion criteria (≤18) and comparable. Values at the last examination under treatment (Visit 5) were 17.7 (6.44) for the DHEA group and 16.8 (5.75) for the placebo group. Both means were still below the inclusion criteria and the placebo group was only slightly worse than the DHEA group. Change from baseline to Visit 5 was 5.0 (6.33) for the DHEA group and 4.1 (6.12) for the placebo group. The minimal difference between the groups was not statistically significant (p = 0.283, Wilcoxon Test with Monte Carlo Approximation). There is no difference between the FAS and the PPS.

Secondary efficacy: The results of secondary efficacy parameters were consistent with primary efficacy results.

Table 1 describes absolute values and change from baseline to Cycle 1 (Visit 3), Cycle 3 (Visit 4), Cycle 6 (Visit 5), and follow up (Visit 6) in FSFI multidimensional self-report questionnaire (component scores [desire, arousal]) in PPS. There was no difference between the FAS and the PPS.

Table 1: FSFI Desire and Arousal not-weighted sum, last observation carried forward (LOCF), and change from baseline: Descriptive statistics by Visit and Treatment – PPS.

		Value at Visit						Change from Baseline					
Treatment	Visit	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
SH K4828A	Visit 1	43	11.9	4.42	2	12.0	18	43	-0.8	4.54	-16	0.0	8
	Visit 2	43	12.7	3.95	2	14.0	18						
	Visit 3	43	18.0	5.09	8	18.0	26	43	5.3	5.63	-7	6.0	22
	Visit 4	43	17.6	6.16	2	19.0	26	43	4.9	5.21	-12	5.0	14
	Visit 5	43	17.7	6.52	2	19.0	30	43	4.9	6.64	-11	5.0	14
	Visit 6	43	17.4	6.54	2	18.0	27	43	4.7	5.65	-13	5.0	14
SH K4828P	Visit 1	41	12.7	3.39	4	13.0	18	41	0.0	3.29	-7	0.0	8
	Visit 2	41	12.7	3.89	2	13.0	18						
	Visit 3	41	15.2	5.11	2	14.0	26	41	2.5	5.36	-15	1.0	15
	Visit 4	41	15.6	5.89	2	16.0	28	41	2.9	5.62	-9	2.0	18
	Visit 5	41	17.4	5.63	2	17.0	29	41	4.7	6.32	-16	4.0	18
	Visit 6	41	16.4	5.69	4	17.0	28	41	3.7	6.11	-14	4.0	16

SH K4828A: DHEA group
SH K4828P: Placebo group

The percentage of successful and satisfactory sexual events per cycle was 42.2% (36.89) at baseline (pretreatment cycle) (median 33.3%) in the DHEA group, and 36.8% (34.65) at baseline (median 28.6%) in the placebo group. During the last treatment cycle (Cycle 6), 67.0% (34.27) (median 75.0%) of the sexual events in the DHEA group and 59.5% (36.06) (median 62.5%) of the sexual events in the placebo group have been rated as successful and satisfactory. This was an absolute increase of 24.9%

(40.90) (median 22.6) of events for the DHEA group and 22.4% (42.68) of events (median 13.8) for the placebo group; the difference between the groups was negligible.

The FSDS-R sum score improved from 30.1 (8.93) to 21.9 (11.51) in the DHEA group and from 29.6 (7.06) to 20.8 (10.55) in the placebo group. This was an improvement from the baseline by 8.0 (9.32) in the DHEA group and by 8.6 (10.52) in the placebo group.

The number of FSEP questionnaires (number of - rated - sexual events) per cycle at baseline (pretreatment cycle) was 3.5 (2.53) (median 3.0) in the DHEA group and 3.4 (2.75) (median 3.0) in the placebo group. During the last treatment cycle (Cycle 6), 4.7 (3.90) (median 4) questionnaires in the DHEA group and 4.3 (3.67) (median 4) questionnaires in the placebo group were filled in. This was an absolute increase of 1.2 (3.23) events (median 1) for the DHEA group and 0.8 (3.04) events (median 0) for the placebo group; the difference between the groups was negligible.

The PGWBI total score did not change in the DHEA group with 96.5 (14.93) at baseline (Visit 2) and 95.2 (18.57) at final (Visit 5) [change −0.3 (16.17)]. In the placebo group, the total score slightly improved from baseline 97.0 (14.08) to final 100.6 (12.65) by 3.5 (17.16).

In the subjective assessment, the numbers of subjects who registered satisfaction with the treatment or improvement were minimal and the same in both the treatment groups.

In a post hoc analysis, the subjects were divided into subpopulations according to their baseline hormone levels of DHEA, DHEA-S, T, and SHBG, and the treatment effects on the low baseline subpopulations were compared. For the group with low baseline DHEA, a significant difference in desire and arousal change to baseline between DHEA group [5.0 (4.24)] and placebo group [1.9 (4.83)] was found ($p = 0.019$). For the subgroups with low DHEA-S, T, and SHBG, no significant differences were observed.

Safety evaluation

The mean duration of exposure to the study drug was 159 days in the DHEA group and 160 days in the placebo group.

A total of 72 (72%) subjects reported at least 1 AE during the study at some time before the final visit; 177 events were reported in all. In the DHEA group, 39 (76.5%) subjects reported a total 104 events. In the placebo group, 33 (67.3%) subjects reported a total of 73 events. The most common AEs in both the treatment groups were nasopharyngitis followed by headache and lower abdominal pain. Headache and lower abdominal pain were both reported more commonly in the DHEA group than in the placebo group. Facial acne is an expected event with DHEA and therefore it did not have to be recorded as an AE. Nevertheless, acne was reported as an AE by 4 subjects in the DHEA group. The only other AEs which were reported by at least 3 DHEA subjects were increased weight and seborrhea. In all, 15 events were reported by at least 2 (4%) DHEA subjects.

No deaths or non-fatal SAEs were reported during the study.

In both the DHEA group and the placebo group, there was 1 subject with severe AEs; all other subjects had mild or moderate AEs. In the DHEA group, 1 subject had severe influenza and severe nasopharyngitis, and in the placebo group, the subject had severe nasopharyngitis. The huge majority of

AEs were present continuously and there was no difference between the treatment groups. There were no AE-induced dose changes in either group. In the DHEA group, 1 subject was recorded as discontinuing the treatment due to AEs, dizziness and nausea. One further DHEA subject discontinued due to preexisting breast tension, but this was not recorded as an AE nor as an AE dropout because it did not worsen after the study treatment started. A third DHEA subject discontinued due to acne, but acne, an expected event with DHEA, was not recorded as an AE or as an AE dropout in this study. There were no discontinuations from the placebo group. Of the 14 DHEA subjects with AEs possibly or probably related to the drug, the most common were reports of acne and seborrhea, and other events that could be expected with either DHEA or OCs. One DHEA subject had an unresolved eczema, one had increased body weight, and one placebo subject had an unresolved decreased blood iron value when the study finished. All other AES resolved at end of the study.

One DHEA subject had a clinically significant leukocyte finding at both baseline and follow-up. One placebo subject at follow-up had a clinically significant iron finding, 1 subject had a clinically significant hemoglobin finding and 1 subject had a clinically significant hematocrit finding.

At both baseline measures 66% of subjects reported no acne at all and the two treatment groups were comparable. By the end of treatment the rate of those in the DHEA group with no acne had dropped to 45% compared to 61% in the placebo group. The rates of minimal, mild and then also moderate acne rose in the DHEA group, but there was no report of severe or extreme acne at any time.

At the Follow-up visit, 3 DHEA and 3 placebo subjects were found to have 'findings in' the cervical smear test. Abnormal/new physical and gynecological examination findings were reported as AEs. Blood pressure, pulse and body weight showed no differences between the treatment groups at baseline, there were minimal changes in various directions during the study and again no clinically relevant change between the last visit on treatment and the Follow-up visit.

One initially unnoticed pregnancy occurred. It can be assumed that the subject continued to take DHEA for 7-8 weeks after conception before she completed the course of DHEA as planned. Likewise she continued to take OC for over 2 months after conception. The details of the course of the pregnancy and the delivery are unknown but the child was healthy.

Both groups had a mean baseline value of vaginal pH just over 4.0 which remained more or less unchanged throughout the study. Only few subjects had a pH above 5 at any time and the maximum values varied.

Clinical pharmacology evaluation

Pharmacokinetic evaluation: In the evaluation of all subjects, the hormone concentration of DHEA in the DHEA-treated group rose from 51 nmol/L at baseline to 155 nmol/L by Visit 3 and remained at that level throughout treatment and fell back to baseline levels by the follow-up visit. The DHEA level of the placebo-treated subjects varied between 45 and 63 nmol/L throughout the study. Likewise, DHEA-S also rose from 5 to 22 nmol/L by Visit 3, staying there, and returning to 6 at the Follow-up visit in the DHEA-treated subjects, while remaining unchanged in the placebo group. Testosterone followed the same pattern, while SHBG dropped more gradually over the full 6 cycles from 230 nmol/L at baseline to 194 nmol/L at Visit 5. By Visit 6, it was still at 191 nmol/L compared to 225 nmol/L in the placebo

group. When interpreting the increases described above, it should be kept in mind that samples were taken at different times relative to the study drug administration.

Overall conclusions

In this exploratory study, results did not show superiority of daily oral 100 mg DHEA over placebo taken for six 28-day menstrual cycles as a concomitant therapy to OCs to alleviate complaints of reduced libido in women with acquired female sexual dysfunction associated with OC use. However, post hoc analysis suggested that subjects with low baseline DHEA values benefited more than those with normal baseline levels. No safety concerns arose during the conduct of the study.