Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	91548	NCT00764881
Study Phase:	IIIb	
Official Study Title:	Multi-center, double-blind, randomized study to investigate the impact of a sequential oral contraceptive containing estradiol valerate and dienogest, SH T00658ID compared to a monophasic contraceptive containing ethinylestradiol and levonorgestrel (Microgynon) over 6 treatment cycles on alleviating complaints of reduced libido in women with acquired female sexual dysfunction (FSD) associated with oral contraceptive (OC) use	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EV/DNG (Qlaira, BAY86-5027)	
Name of Active Ingredient:	Estradiol valerate (EV) and dienogest (DNG)	
Dose and Mode of Administration:	The medication was encapsulated for blinding purpose. Daily oral administration of one capsule of BAY 86-5027 (EV/DNG) for 28 days (total) per cycle in the sequential 4-phasic regimen as summarized below in Table 1.	
Reference Therapy/Placebo		
Reference Therapy:	Ethinylestradiol (EE) + levonorgestrel (LNG) (Microgynon)	
Dose and Mode of Administration:	The medication was encapsulated for blinding purpose. Daily oral administration of 1 capsule of 0.03 mg EE + 0.15 mg LNG for 21 days, followed by 1 capsule placebo for 7 days (28 days total per cycle) (monophasic 21-day regimen) (Table 2).	

Table 1: Sequential 4-phasic regimen

Phase	Day	Dose
1	1-2	3.0 mg EV
2a	3-7	2.0 mg EV + 2.0 mg DNG
2b	8-24	2.0 mg EV + 3.0 mg DNG
3	25-26	1.0 mg EV
4	27-28	Placebo

There were no capsule-free intervals between cycles.

Table 2: Monophasic 21-day regimen

Day	Dose
1-21	0.03 mg EE + 0.15 mg LNG
22-28	Placebo

	There were no capsule-free intervals between cycles.	
Duration of Treatment:	Six treatment cycles, each of which was 28 days long (a total of 168 days).	
Studied period:	Date of first subjects' first visit:	29 JAN 2009
	Date of last subjects' last visit:	20 JUL 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 2 (dated 18 DEC 2008) updated the clinical global impression (CGI) questionnaire with an additional question for the subject regarding satisfaction with sexuality during treatment. Amendment no. 3 (dated 15 JUN 2009) was a local amendment for Thailand. Since Thailand is in a warm climate (Climate Zone IV), the protocol was amended to include that refrigeration (2 to 8˚C) was required if study medication could not be stored at room temperature below 25˚C.	
Study Centre(s):	The study was conducted in 26 centers in 7 countries: 7 in Austria; 6 in Australia; 4 in Italy; 3 in Belgium; 2 in Spain; 2 in Germany; 2 in Thailand.	
Methodology:	The study was a multicenter, double-blind, randomized, active control, parallel-group, 2-arm study in healthy female subjects. The study comprised of a screening visit, an admission (baseline) visit, 3 treatment visits (Cycles 2, 4, and 6), and a final visit. The final visit took place at premature discontinuation or after cycle 6 with in 12 to 19 days after end of study medication. Following randomization in a 1:1 ratio into either the EV/DNG or EE/LNG treatment arms, the first dose of study drug was taken after completion of the last active pill of the cycle pack of the previous oral contraceptive (OC). The following variables were assessed: Efficacy: Self-reported questionnaires – Female sexual function index (FSFI), female sexual distress scale (FSDS-R), quality of life enjoyment and satisfaction questionnaire (Q-LES-Q) short version, psychological general well-being index (PGWBI), and atrophy Symptoms Questionnaire (ASQ); investigator assessments – CGI and vaginal health assessment (VHA). Safety: Adverse events (AEs) and serious AEs (SAEs), general physical and gynecological examinations, cervical smears, vital signs: heart rate and blood pressure, body weight, body mass index (BMI), and vaginal pH measurements.	
Indication/ Main Inclusion Criteria:	Indication: Oral contraception Main Inclusion criteria: Subjects on an oral contraceptive (OC) who were: • Suffering from acquired OC-associated female sexual dysfunction (FSD) for at least 3 months (but no longer than 1 year) • Willing to continue OC use and switch to EV/DNG or EE/LNG	

	• Found to have a combined score on the sexual desire and arousal domains of the Female Sexual Function Index (FSFI) questionnaire of 18 or below at Screening and Baseline.
Study Objectives:	Primary: The primary objective of this study was to show noninferiority of BAY 86-5027 (EV/DNG) to Microgynon (EE/LNG) on libido in women with acquired FSD associated with OC use. Secondary: The secondary objectives of this study were: • To evaluate other domains of the FSFI and other self-reported measures (FSDS, Q-LES-Q, PGWBI) in order to explore further effects of EV/DNG on female sexual function and general psychological status • To evaluate Clinical Global Impression assessment • To further evaluate the safety profile of EV/DNG • To evaluate vaginal effects by: vaginal pH measurements, the Atrophy Symptom Questionnaire, and the Vaginal Health Assessment
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the change from Baseline to Cycle 6 in the not weighted sum of questions 1 to 6 of the FSFI sexual desire and the sexual arousal component scores, defined as the total of questions 1 to 6 of the FSFI, in the full analysis set and the per protocol set. Efficacy (Secondary): Secondary efficacy variables were: • The mean absolute values of FSFI Domain score (desire) at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Domain score (desire) • The mean absolute values of FSFI Domain score (arousal) at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Domain score (arousal) • The mean absolute values of FSFI Domain score (lubrication) at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Domain score (lubrication) • The mean absolute values of FSFI Domain score (orgasm) at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Domain score (orgasm) • The mean absolute values of FSFI Domain score (satisfaction) at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Domain score (satisfaction) • The mean absolute values of FSFI Domain score (pain) at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Domain score (pain) • The mean absolute values of FSFI Total score at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSFI Total score • The mean absolute values of FSDS-R Total score at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in FSDS-R Total score • The mean absolute values of Life Enjoyment and Satisfaction (Q-LES-Q) (short version) Total score at baseline and Cycle 6, and the

	mean change from baseline to Cycle 6 in Q-LES-Q (short version) Total score • The mean absolute values of Psychological General Well-Being (PWGBI) Global Score at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI Global Score • The mean absolute values of PWGBI-Anxiety at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI-Anxiety • The mean absolute values of PWGBI-Depressed mood at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI- Depressed mood • The mean absolute values of PWGBI-Positive well-being at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI- Positive well-being • The mean absolute values of PWGBI-Self-control at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI-Self-control • The mean absolute values of PWGBI-General health at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI-General health • The mean absolute values of PWGBI-Vitality at baseline and Cycle 6, and the mean change from baseline to Cycle 6 in PWGBI-Vitality • Percentage of subjects with improvement in the Investigator's assessment in Clinical Global Impression (CGI) at Cycle 6 • Percentage of subjects with improvement in the Subject's assessment in Clinical Global Impression (CGI) at Cycle 6 • Vaginal effects evaluated by vaginal pH at Cycle 6, mean absolute values in Atrophy Symptom Questionnaire (ASQ) at baseline and Cycle 6, and mean change from baseline to Cycle 6 in ASQ, mean absolute values in Vaginal Health Assessment (VHA) at baseline and Cycle 6, and mean change from baseline to Cycle 6 in VHA • Number of bleeding/spotting days in Reference periods 1 and 2 • Number of bleeding/spotting episodes in Reference periods 1 and 2 • Mean length of bleeding/spotting episodes in Reference periods 1 and 2 • Maximum length of bleeding/spotting episodes in Reference periods 1 and 2 • Difference in duration between longest and shortest bleeding/spotting episodes in Reference periods 1 and 2 • Number of spotting only days in Reference periods 1 and 2 • Number of spotting only episodes in Reference periods 1 and 2 • Mean length of spotting only episodes in Reference periods 1 and 2 • Maximum length of spotting only episodes in Reference periods 1 and 2 • Difference in duration between longest and shortest spotting-only episodes in Reference periods 1 and 2 • Percentage of subjects with/without withdrawal bleeding at Cycles 1, 3,and 6 • Length of withdrawal bleeding episodes at Cycle 1, 3, and 6 • Maximum intensity of withdrawal bleeding episodes at Cycles 1, 3, and 6 • Percentage of subjects by maximum intensity of withdrawal bleeding episodes at Cycles 1, 3, and 6 • Onset of withdrawal bleeding episodes at Cycles 1, 3, and 6 • Percentage of subjects with presence or absence of intracyclic bleeding at Cycles 1, 3, and 6 • Number of intracyclic bleeding episodes at Cycles 1, 3, and 6

	• Maximum length of intracyclic bleeding episodes at Cycles 1, 3, and 6 • Number of intracyclic bleeding days at Cycles 1, 3, and 6 • Percentage of subjects by maximum intensity of intracyclic bleeding episodes at Cycles 1, 3, and 6 • Percentage of subjects with at least 1 intracyclic bleeding episode Safety: AEs and SAEs, general physical and gynecological examinations, cervical smears, vital signs: heart rate and blood pressure, body weight, body mass index (BMI), and vaginal pH measurements
	Other: Questions regarding change of partner and relationship/partnership satisfaction and a subjective assessment on satisfaction with the study treatment were analyzed.
Statistical Methods:	Efficacy (Primary): The individual change in sexual desire and arousal component scores of the FSFI questionnaire were calculated from Baseline to Cycle 6 as $\Delta S_6 = S_6 - S_0$, where S_6 is the not weighted sum of sexual desire and arousal component scores (sum of questions 1 - 6) over Cycle 6 and S_0 is the respective value at Baseline. Higher values at the end, i.e., positive differences (ΔS_6), show improvement. To show noninferiority of BAY 86-5027, the null-hypothesis H_{01}: true median ΔS_6 (BAY 86-5027) ≤ true median ΔS_6 (Microgynon) - Δni was tested against the alternative hypothesis H_{A1}: true median ΔS_6 (BAY 86-5027) > true median ΔS_6 (Microgynon) – Δni, where Δni stands for the non-inferiority threshold value of clinical relevance. Δni was defined to be 5. The hypothesis H_{01} was rejected if the distribution free 95% confidence interval based on the normal approximation of the Mann-Whitney statistic of the difference ΔS_6 (BAY 86-5027) - ΔS_6 (Microgynon) lied entirely above - Δni. In case of a positive noninferiority test result, BAY 86-5027 was to be compared to Microgynon for superiority. The null hypothesis H_{02}: true median ΔS_6 (BAY 86-5027) ≤ true median ΔS_6 (Microgynon) was tested against the alternative hypothesis H_{A2}: true median ΔS_6 (BAY 86-5027) > true median ΔS_6 (Microgynon) The hypothesis H_{02} was rejected if the distribution free 95% confidence interval (CI) based on the normal approximation to the distribution of the Mann-Whitney statistic of the difference ΔS_6 (BAY 86-5027) - ΔS_6 (Microgynon) lied entirely above 0. In addition, to better understand a potential effect of pain during vaginal penetration on libido, a subgroup analysis of the primary efficacy variable was performed. One subgroup was defined by a score of 1 or 2 in at least one of questions 17, 18, or 19 of the FSFI

	questionnaire completed at the Baseline. The other subgroup was the complement to this subgroup. Efficacy (Secondary): Secondary efficacy variables were analyzed as exploratory endpoints. Descriptive statistics were employed to analyze the following questionnaire scores as well as their respective changes from baseline scores: FSFI multidimensional self-report questionnaire (domain scores and full scale scores); Total FSDS-R score; Q-LES-Q score for metric data; PGWBI subscale values and total sum score; ASQ score; and VHA score. Frequency tables displayed CGI scores, vaginal pH values; and 2 items scored separately on the Q-LES-Q–satisfaction with medication and overall life satisfaction and control. Safety: Safety parameters were analyzed by summary statistics for numerical data and by frequency tables for categorical data.
	Pharmacokinetics : Not applicable Other : Global assessment of efficacy by the investigator and by the subject was analyzed by frequency tables.
Number of Subjects:	Planned: 216 (108 subjects in each treatment arm). Analyzed: 217 subjects (192 subjects completed the study).

Study Results

Results Summary — Subject Disposition and Baseline

Out of 276 subjects screened, there were 59 screening failures. A total of 217 randomized 1:1 of which 1 subject never received treatment, 3 subjects have no observations, and 213 were treated (EV/DNG = 106; and EE/LNG = 107 subjects). A total of 191 subjects completed study course: EV/DNG = 92; EE/LNG = 99 subjects. Overall for the full analysis set (FAS), there were no significant differences across the treatment groups with regard to any of the demographic or baseline characteristics: age, ethnic group, body weight, height, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, or alcohol consumption. Specifically, median age was 28 (EE/LNG) to 30 (EV/DNG) years, ethnic group was more than 80% Caucasian, median height was 165 cm and median body weight was 61.0 (EE/LNG) to 61.8 (EV/DNG) kg, median BMI was 22.160 (EV/DNG) to 22.450 (EE/LNG) kg/m^2. For both treatment groups, mean body weight and BMI remained relatively stable throughout the study increasing by less than 0.5 kg and 0.1 kg/m^2, respectively.

Only slightly more than 6.5% of the subjects (i.e., 7 subjects in either the EV/DNG [6.6%] or EE/LNG [6.5%] group) consumed alcohol on a regular basis.

Subjects in both treatment groups had equivalent gynecological histories. The mean (SD) age at menarche was 13.2 ± 1.4 years. Approximately 50% of the subjects had never been pregnant and more than 85% had never had an abortion.

Subjects in both treatment groups had equivalent menstrual histories. More than 90% of the subjects experienced a regular cycle in the past 30 days. More than 50% of the subjects (124 [58.2%]) experienced normal bleeding intensity on average; more than 90% (207 [97.2%]

subjects) reported no intracyclic vaginal bleeding or menorrhagia (212 [99.5%] subjects); and more than 85% (184 [86.4%]) reported no incidence of dysmenorrhea.

Only 2 subjects (0.9%), 1 subject (0.9%) in each treatment group did not use any contraceptive method within 30 days of Visit 1. With the exception of 1 subject (0.9%) in the EE/LNG group who used Nuvaring as her method of contraception, the other 210 (98.6%) subjects chose an oral contraceptive as her method of contraception.

Results Summary — Efficacy

Efficacy conclusions were as follows:

Primary efficacy variable – Changes from Baseline to Cycle 6 in the total of questions 1 to 6 of the FSFI sexual desire and the sexual arousal component scores

- EV/DNG was noninferior but not superior to EE/LNG

Secondary efficacy variables:

- There was no meaningful difference between EV/DNG and EE/LNG treatment groups in the following:
  - FSFI domain scores desire, arousal, lubrication, orgasm, satisfaction, pain, and total score.
  - FSDS-R total score, Q-LES-Q total score and Q-LES-Q overall life satisfaction and contentment score
  - PGWBI scores for anxiety, positive well-being, self-control, general health, vitality, and global score
  - Vaginal pH
  - ASQ sum score
  - VHA sum score

Other efficacy variables

- There was no meaningful difference between EV/DNG and EE/LNG treatment groups in the following:
  - Subject satisfaction assessment questionnaire with regard to treatment planned to be used in the future.
  - Bleeding pattern: number of bleeding/spotting days, number of bleeding/spotting episodes, mean length of bleeding/spotting episodes, maximum length of bleeding/spotting episodes, maximum length of spotting-only episodes, range of length of spotting-only episodes.
  - Cycle control parameter: mean length of withdrawal bleeding episodes, maximum intensity of withdrawal bleeding episodes, onset of withdrawal bleeding episodes.

- There was some indication of a meaningful difference in favor of the EE/LNG treatment group in the following:
  - Bleeding pattern: shorter range of length of bleeding/spotting episodes from Reference Period 1 to 2, fewer spotting only days, fewer spotting only episodes in Reference Period 1, shorter mean length of spotting-only episodes.
  - Cycle control parameter: fewer subjects experienced intracyclic bleeding; and of those who did experience intracyclic bleeding, more subjects reported the lowest maximum intensity (spotting), there was a slightly lower number of intracyclic bleeding episodes, shorter maximum length of intracyclic bleeding episodes, and fewer intracyclic bleeding days.

Results Summary — Safety

Both study drugs were well-tolerated. There were no deaths and few SAEs. Slightly over one-third of the subjects reported treatment-emergent adverse events (TEAEs). Women enrolled in the EV/DNG group experienced twice as many TEAEs as subjects enrolled in the EE/LNG group. This may partly be attributed to the fact that randomization was across the study and not by center. Therefore, a center effect cannot be excluded. However, the percentage of women experiencing TEAEs assessed as being causally related to the study medication was comparable in both groups.

SAEs were reported from subjects on study drug, of which all were experienced by subjects (3.8%) in the EV/DNG group: deep vein thrombosis (after a ski accident and subsequent immobilization), acute appendicitis, and breast cancer. One EE/LNG subject experienced the SAE gastroenteritis after randomization, but before she took study drug. One pregnancy occurred prior to randomization and was reported as an SAE, because the subject had an elective abortion. Of these 5 SAEs, 1 (deep vein thrombosis) was determined to have a causal relationship to study drug. This subject had been taking a COC (2 mg Ciproterone and 35 mcg EE) from FEB 2008 to MAY 2009 before inclusion into the trial.

With respect to the 213 subjects enrolled in the FAS, 112 subjects (52.6%) experienced 298 medical/surgical events distributed by treatment group as follows: EV/DNG = 66 (62.3%) subjects and 175 events and EE/LNG = 46 (43.0%) subjects and 123 events.

At least 50% of these subjects experienced TEAEs of mild intensity. Few subjects experienced severe TEAEs: 7 (6.6%) EV/DNG subjects and 5 (4.7%) EE/LNG subjects.

Six subjects experienced AEs that led to discontinuation of study drug: abdominal distension and withdrawal bleeding in 1 subject, urticaria, acne, deep vein thrombosis (SAE), and breast cancer (SAE) in the EV/DNG group, and infectious mononucleosis in the EE/LNG group. Of these AEs, abdominal distension, withdrawal bleeding, acne, and deep vein thrombosis were judged to be causally related to study drug.

Of the 7 subjects (4 EV/DNG subjects and 3 EE/LNG subject) who were determined to have abnormal cervical smears at Cycle 6, three subjects (2 EV/DNG subjects and 1 EE/LNG subject) had abnormal findings that were determined to be clinically significant. For both of the cases that occurred in the EV/DNG group follow-up examinations resulting in a "normal" outcome were performed. So far, the attempts by the site to contact the subject of the EE/LNG group have failed and therefore no follow-up information is available for this case.

Conclusion(s)

This study of 217 subjects invalidates the assumption that anti-androgenic progestogens like DNG are worse with regard to FSD compared to androgenic progestogens like LNG. It could be demonstrated that EV/DNG is noninferior to EE/LNG at improving FSD demonstrated by an increase in the FSFI sexual desire and arousal component scores. Both, EV/DNG and EE/LNG improved OC-associated FSD to a similar extent. In particular, no clinically meaningful difference between the 2 treatment groups could be shown, neither with regard to the primary endpoint, nor regarding the several secondary efficacy parameters that were evaluated during the study. Both treatments were safe and well tolerated.

Publication(s):	None		
Date Created or Date Last Updated:	12 APR 2012	Date of Clinical Study Report:	02 FEB 2011

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Natazia
Brand/Trade Name(s) ex-US	Qlaira, Klaira, Qlair, Qlairista
Generic Name	Estradiol valerate, Dienogest
Main Product Company Code	BAY86-5027
Other Company Code(s)	SH T 00658 ID
Chemical Description	Estra–1,3,5(10)–triene–3,17β–diol–17–valerate (WHO) 19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-17α-Cyanomethyl-17β-hydroxy-estra-4,9-dien-3-one (CAS)
Other Product Aliases	Estradiol 17–valerate Estradiol 17β–valerate Estra–1,3,5(10)–triene–3,17–diol (17β), 17–pentanoate 1,3,5(10)–Estratriene–3,17β–diol–17–valerate ZK 5104 17α-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC) 17β-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile (17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile ZK00037659 FS-10101-N

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