Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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

<table>
<tr><th colspan="3">Study Design Description</th></tr>
<tr><td>Study Sponsor:</td><td colspan="2">Bayer HealthCare AG</td></tr>
<tr><td>Study Number:</td><td>91550 (310787)</td><td>NCT00778609</td></tr>
<tr><td>Study Phase:</td><td colspan="2">IIIb</td></tr>
<tr><td>Official Study Title:</td><td colspan="2">A multicenter, randomized, double-blind, active-controlled, parallel group, 2-arm study to investigate the effect of estradiol valerate/dienogest compared to Microgynon on hormone withdrawal associated symptoms in otherwise healthy women after 6 cycles of treatment</td></tr>
<tr><td>Therapeutic Area:</td><td colspan="2">Women’s Healthcare</td></tr>
<tr><td colspan="3">Test Product</td></tr>
<tr><td>Name of Test Product:</td><td colspan="2">EV/DNG (Qlaira, BAY86-5027)</td></tr>
<tr><td>Name of Active Ingredient:</td><td colspan="2">Estradiol valerate (EV) and dienogest (DNG)</td></tr>
<tr><td>Dose and Mode of Administration:</td><td colspan="2">The test drug was encapsulated for blinding purposes. Daily oral administration of one capsule for 28 days per cycle in the respective treatment period; no pill-free interval.

Sequential 4-phasic regimen

<table>
<tr><th>Phase</th><th>Day</th><th>Dose</th></tr>
<tr><td>1</td><td>1-2</td><td>3.0 mg EV</td></tr>
<tr><td>2a</td><td>3-7</td><td>2.0 mg EV + 2.0 mg DNG</td></tr>
<tr><td>2b</td><td>8-24</td><td>2.0 mg EV + 3.0 mg DNG</td></tr>
<tr><td>3</td><td>25-26</td><td>1.0 mg EV</td></tr>
<tr><td>4</td><td>27-28</td><td>Placebo</td></tr>
</table></td></tr>
<tr><td colspan="3">Reference Therapy/Placebo</td></tr>
<tr><td>Reference Therapy:</td><td colspan="2">Microgynon</td></tr>
<tr><td>Dose and Mode of Administration:</td><td colspan="2">The reference drug was encapsulated for blinded purposes. Daily oral administration of one capsule for 28 days per cycle in the respective treatment period; no pill-free interval.

Monophasic 21-day regimen

<table>
<tr><th>Day</th><th>Dose</th></tr>
<tr><td>1-21</td><td>0.03 mg ethinylestradiol (EE) + 0.15 mg levonorgestrel (LNG)</td></tr>
<tr><td>22-28</td><td>Placebo</td></tr>
</table></td></tr>
<tr><td>Duration of Treatment:</td><td colspan="2">Approximately 6 months (6 cycles; each cycle of 28 days).</td></tr>
<tr><td rowspan="2">Studied period:</td><td>Date of first subjects’ first visit:</td><td>03 DEC 2008</td></tr>
<tr><td>Date of last subjects’ last visit:</td><td>28 DEC 2010</td></tr>
</table>

Premature Study Suspension / Termination:	No
Substantial Study Protocol Amendments:	There were 3 global amendments (Amendments 1, 2 and 5) and 2 local amendments (Amendments 3 and 4) to the study protocol. Amendment no. 1 (dated 15 SEP 2008) was globally implemented before the first subject's first visit. It specified the following modifications: • Changes to inclusion, exclusion, or withdrawal criteria: ➢ Subjects now needed to have been on an LNG containing OC for at least 3 cycles before visit 1. ➢ A new withdrawal criterion was added. Subjects who missed one capsule by more than 12 hours on Days 18 - 24 in more than two cycles were to be withdrawn. • Changes to intake schedule: ➢ The fixed time window for daily study drug intake was changed to study drug intake at the same time every day. ➢ Advice for first study drug intake was changed. • Changes to safety variables: urine pregnancy test: ➢ There was an additional urine pregnancy test at the follow-up visit. ➢ A urine pregnancy test was no longer considered necessary at screening (visit 1). • Changes to data management and monitoring: ➢ The standard text regarding monitoring was amended to reflect the possibility that study drug could be destroyed at the site after drug accountability had been performed. ➢ The source documentation was clarified. Full date of birth was documented in the subject files for source data verification. ➢ Certain documentation such as visit dates were added to support monitoring of trial progress by the sponsor. ➢ The structure of subject identification number changed and consisted of 9 (instead of 6) digits. ➢ A sentence was added to clarify the procedures in case of re-started cycles. Amendment no. 2 (dated 02 APR 2009) was globally implemented approximately 3 months after the first subject's first visit. It referred to in-/exclusion criteria that were modified to avoid a very high rate of screening failure as had been observed in a similar study. This had been due to an inclusion threshold that had excluded many subjects having hormone withdrawal associated symptoms from participating in the study. • Changes to in-/ exclusion criteria: ➢ The inclusion requirement for pain visual analog scale (VAS) changed. Previously, subjects had to display an average VAS score of at least 35 mm during the 7-day hormone free interval. As of Amendment 2, only the 3 days during this period with most pain on the VAS were taken into consideration for the average VAS score. ➢ The maximum age for smokers to be eligible for this study was changed from 30 to 35 years. ➢ Additional previous oral contraceptives (gestodene [GSD]

	and desogestrel [DSG]) were allowed. • Clarification of statistical methods: ➢ The wording of the statistical assumptions for the primary variable, the VAS, was clarified. • Clarification of procedures for safety variables: ➢ Procedures for blood pressure measurements were specified to ensure consistent blood pressure readings. ➢ Procedures for performing and reporting pregnancy tests were clarified. • Clarifications regarding prior and concomitant medication: ➢ Recommendation regarding rescue medication was added. For clarification, it was added that Ibuprofen was preferred as rescue medication for all other pain during the study (not just for pelvic pain and headache). ➢ Guidance regarding prior and concomitant medication was added. The use of antibiotics and some psychotropic drugs can reduce the bioavailability of hormonal contraceptives and thus efficacy. Therefore, women on such short-term treatment were to use back-up contraception (any additional non-hormonal method of contraception except the calendar or temperature method) in addition to the study drug until 9 days after discontinuation of the respective treatment. • Changes to visit schedule: ➢ The amendment added an update of menstrual history at visit 2. • Clarification for diary: ➢ The time-point for starting daily diary entries was clarified. • Changes to start of baseline cycle: ➢ The definition of the start of the baseline cycle was clarified. Amendment no. 3 (dated 30 JUL 2009) specified the modification for Thailand only approximately 6 months after the first subject's first visit. It clarified that Thailand was the only country where the study medication could not be stored at room temperature due to Thailand's climate. There, study medication was to be stored in a refrigerator (2 - 8ºC). Amendment no. 4 (dated 20 OCT 2009) was implemented for germany only and clarified the underlying assumptions that sample size did not need to change with protocol amendment 2; this clarification had been requested by the Ethics Committee for Germany. Amendment no. 5 (dated 21 OCT 2009) was implemented globally approximately 9 months after the first subject's first visit. It specified the following changes: • The sponsor decided that the 2 hormone withdrawal associated symptoms, headache and pelvic pain used for the primary endpoint, so far would be combined to form a single primary variable. As a result, the number of subjects needed for this study was reduced considerably. This amendment introduced the respective changes to the study protocol. • The inclusion requirement regarding cervical smear was clarified.

	Women with atypical squamous cells of undetermined significance could be included if they had a negative human papilloma virus test result.
Study Centre(s):	Fifty-one (51) study centers randomized subjects in 9 countries: Australia (10), Finland (4), France (8), Germany (11), Mexico (5), Spain (4), Switzerland (4), Thailand (2), the United Kingdom (3). Thirteen (13) further centers in 6 countries recruited but did not randomize subjects: Australia (1), Finland (1), France (5), Spain (2), Thailand (1), the United Kingdom (3).
Methodology:	In this multicenter, randomized, double-blind, active-controlled, parallel-group, 2-arm study, the subjects were randomized to receive either Qlaira or Microgynon. The first dose was taken the day after taking the last active pill of the previous oral contraceptive (OC) after the admission visit. On the first day of pill taking of the next OC pack after visit 1, the baseline cycle started. The subject started to make daily diary entries and performed VAS assessments of pelvic pain and headache. Visit 2 took place between days 12 and 19 of the cycle following this baseline cycle. Baseline QoL questionnaires were completed as scheduled. Enrollment into the study and assignment of a randomization number took place at this visit after all inclusion/exclusion criteria had been met. Subjects were assigned to either stratum 1 or stratum 2, depending on their baseline VAS values for pelvic pain and headache. Throughout the course of the study, the subject was seen by the investigator according to a set schedule, to ensure compliance and adequate AE reporting. The visits took place in the middle of the treatment cycles between days 12 and 19 (inclusive) of the medication blister pack. After the end of the medication phase, a final examination was performed within 12 - 19 days (inclusive) in order to ensure that the subject remained healthy. The primary efficacy variable (hormone withdrawal associated symptoms pelvic pain and headache) was captured using the VAS. For secondary efficacy, frequency and intensity of other hormone withdrawal associated symptoms were recorded for various parts of the subject's cycles. Rescue medication consumption (Ibuprofen), bleeding pattern and cycle control were documented on subject diaries. Quality of life (QoL) questionnaires were also used: Psychological General Well-Being Index (PGWBI), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and Clinical Global Index (CGI). Safety parameters included assessment of adverse events (AEs), physical and gynecological examination, cervical smears, and vital sign measurements.
Indication/ Main Inclusion Criteria:	Indication Oral contraception Main Inclusion Criteria Women aged between 18 and 50 years (smokers ≤35 years) using an LNG, GSD, or DSG containing OC in a 21-day regimen, who were willing to switch to one of the two study drugs (EV/DNG or Microgynon). Being otherwise healthy, subjects who had at least one of the hormone withdrawal associated symptoms headache or pelvic pain, at least of moderate intensity (defined as an average of the 3

	highest VAS values during cycle days 22 - 28 of at least 35 mm) were included.
Study Objectives:	Overall: To show superiority of Qlaira over Microgynon on hormone withdrawal associated symptoms after 6 cycles of treatment.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the change of pelvic pain (stratum 1) or the change of headache (stratum 2) as determined by the change of average of the 3 highest values on a VAS during cycle days 22 to 28 from baseline to cycle 6. Efficacy (Secondary): Secondary efficacy variables were: • Rescue medication consumption, baseline to cycle 6 • Frequency and intensity of other hormone-related symptoms (bloating or swelling, breast tenderness, and nausea or vomiting) during cycle days 22 to 28, baseline to cycle 6 • Prevalence of individual hormone-related symptoms during cycle days 1 to 21, baseline to cycle 6 • Prevalence of individual hormone-related symptoms during hormone-free interval, i.e., cycle days 27+28 for EV/DNG capsules and cycle days 22 to 28 for the comparator • Change in average of the 3 highest VAS values of the hormone withdrawal associated symptoms pelvic pain or headache during cycle days 22 to 28 from baseline to cycle 3 • Bleeding pattern and cycle control • Quality of life (QoL) questionnaires Safety: Assessment of adverse events (AEs), physical and gynecological examination including a cervical smear, pregnancy testing, and vital sign measurements (blood pressure, heart rate, body weight. and body mass index [BMI]).
	Other: Documentation of back up contraception.
Statistical Methods:	Efficacy (Primary): The primary efficacy variable was evaluated using a two-way analysis of variance (ANOVA) model with treatment and pain strata (headache and pelvic pain) as factors and a two-sided type I error of 0.05. Efficacy (Secondary): The secondary efficacy variables, rescue medication consumption, hormone-related symptoms (bloating or swelling, breast tenderness, and nausea or vomiting) were evaluated for the baseline, cycle 3, and cycle 6. All secondary efficacy variables were analyzed using descriptive statistics. Safety: All safety variables were analyzed using descriptive statistics.

	Other : Back-up contraceptive methods used were analyzed by descriptive methods.
Number of Subjects:	Planned: Screening until 440 were randomized; 308 to complete treatment. Analyzed: 441 (safety analysis set [SAF]): 223 EV/DNG and 218 EE/LNG (Microgynon) 427 (full analysis set [FAS]): 217 EV/DNG and 210 EE/LNG (Microgynon) 286 (per protocol set [PPS]):146 EV/DNG and 140 EE/LNG (Microgynon)

Study Results

Results Summary — Subject Disposition and Baseline

Of the 655 subjects who were screened, 449 were randomized in a double-blind fashion: 226 subjects to treatment with EV/DNG (study drug) and 223 to treatment with Microgynon (comparator). Of all the randomized subjects, 3 in the EV/DNG group and 5 in the Microgynon group did not receive any study medication, leaving 223 EV/DNG subjects and 218 Microgynon subjects who actually received treatment and constituted the SAF used for the safety analysis. The FAS used for the primary efficacy analysis consisted of 217 EV/DNG subjects and 210 Microgynon subjects, excluding 6 subjects randomized to EV/DNG and 8 subjects randomized to Microgynon as their site was closed early and reported to the health authority for serious non-compliance with the protocol and ICH-GCP. One subject randomized to EV/DNG actually received Microgynon by mistake and was analyzed in the EV/DNG group for efficacy (FAS and PPS) and in the Microgynon group for safety (SAF).

Overall, 40 subjects on EV/DNG (17.9%) and 38 subjects on Microgynon (17.4%) prematurely discontinued the study medication; 183 subjects completed EV/DNG treatment and 180 subjects completed Microgynon treatment as planned.

A total of 155 subjects (77 EV/DNG and 78 Microgynon subjects) were excluded from the PPS due to major protocol deviations. The PPS consisted of 286 subjects (146 EV/DNG and 140 Microgynon subjects).

Demographic and baseline data of subjects in the SAF were similar between treatment groups. The race of 236/441 subjects overall (53.5%) was described as Caucasian, for 104 (23.6%) as Hispanic, for 60 (13.6%) as Asian, for 1 (0.2%) as Black, and was not documented for 40 (9.1%; note that in some trial countries, collection of data regarding race is not permitted). Their median age was 28 years, with an overall range from 18 to 48 years. Median body weight was 61 kg in the EV/DNG group and 62 kg in the Microgynon group (overall range: 39 to 101 kg), and median height was 163 cm in the EV/DNG group and 164 cm in the Microgynon group (overall range: 146 to 186 cm). The median BMI was 22.9 kg/m^2 in the EV/DNG group and 23.3 kg/m^2 in the Microgynon group, with an overall range of 14.7 to 32.0 kg/m^2.

Overall, medical history findings, menstrual and gynecological history appeared balanced between treatment groups. Most subjects reported a regular cycle at screening (215/223 subjects [96.4%] in the EV/DNG group and 214/218 subjects [98.2%] in the Microgynon group) and an average cycle length of 28 days (EV/DNG: 197/223 [88.3%]; Microgynon: 197/218 [90.4%]). Most subjects experienced dysmenorrhea (EV/DNG: 151/223 [67.7%];

Microgynon: 154/218 [70.6%]).

There was no notable difference between demographic and baseline data for the SAF and the FAS or PPS.

Results Summary — Efficacy

Overall, improvements compared to baseline were seen in both treatment groups over the course of the study for most efficacy variables. For the primary efficacy variable, this improvement was statistically significantly greater for EV/DNG than for Microgynon. Based on these results for the change of the 3 highest VAS values from baseline to cycle 6, superiority of EV/DNG vs Microgynon in reducing pelvic pain or headache could be concluded. Most, but not all, secondary efficacy variables showed numerically greater improvements for the EV/DNG than for the Microgynon group. This conclusion is based on the following findings:

- The reduction between baseline and cycle 6 in the individual change of pelvic pain or headache as determined by the change of average of the 3 highest VAS values during cycle days 22 to 28 (primary efficacy variable, FAS) was 47.70 ± 29.39 mm (mean ± standard deviation [SD]) in the EV/DNG group and thus greater than that in the Microgynon group (34.47 ± 25.67 mm). A two-way ANOVA model with treatment and pain strata (headache and pelvic pain) as factors yielded an F value of 22.4509 for the comparison of EV/DNG vs Microgynon, with a p-value <0.0001. Thus, the difference between the treatment groups in reduction of pain (headache and pelvic pain) on the VAS between baseline and cycle 6 was highly statistically significant. Results for the PPS were consistent with those for the FAS.

- Using only the highest VAS values during cycle days 22 to 28 (instead of the average of the 3 highest values), results were consistent with those for the primary efficacy analysis, i.e., showing a statistically significantly greater reduction between baseline and cycle 6 for EV/DNG than for Microgynon (mean ± SD 48.07 ± 33.03 mm in the EV/DNG group and 34.28 ± 29.08 mm in the Microgynon group; 2-way ANOVA: F = 18.8487, p <0.0001).

- These results of the primary efficacy variable after 3 months (mean ± SD reduction between baseline and cycle 3: 44.98 ± 26.65 mm in the EV/DNG group and 28.27 ± 25.65 mm in the Microgynon group) were similar to those for the primary efficacy evaluation, suggesting that most of the treatment effect of EV/DNG and Microgynon appears within the first 3 months of treatment.

- Responder analyses evaluating certain categories of relative and absolute decrease in VAS scores without increases in rescue medication supported the results for the primary efficacy variable, with consistently numerically more EV/DNG subjects than Microgynon subjects showing the respective decreases.

- Rescue medication use decreased between baseline and cycle 6 in both groups, during cycle days 1 - 21 as well as during cycle days 22 - 28, with numerically greater decreases in the EV/DNG than in the Microgynon group. Mean ± SD changes between baseline and cycle 6 for cycle days 1 - 21 were 1.4 ± 7.7 tablets for EV/DNG and -0.4 ± 6.5 tablets for Microgynon, resulting in a mean difference between groups of 1.001 tablets, with a 95% confidence interval (CI) of 2.482 - 0.479. Mean ± SD changes between baseline and cycle 6 for cycle days 22 - 28 were -3.5 ± 6.3 tablets for EV/DNG and -1.8 ± 6.0 tablets for Microgynon, resulting in a mean difference between groups of 1.762 tablets, with a 95% confidence interval (CI) of -3.04 - (-0.484) that excluded zero.

- Between baseline and cycle 6, a numerical reduction in the mean number of days with at least moderate pain or intensity of other hormone-related symptoms (headache, pelvic pain, bloating or swelling, breast tenderness, and nausea or vomiting) during cycle days 22 to 28 could be seen. For headache (EV/DNG: mean ± SD -2.3 ± 2.4 days;

Microgynon: -1.6 ± 2.2 days), pelvic pain (EV/DNG: mean ± SD -2.1 ± 2.1 days; Microgynon: -1.5 ± 2.2 days) and bloating or swelling (EV/DNG: mean ± SD -0.8 ± 1.9 days; Microgynon: -0.4 ± 1.8 days), the mean reduction was numerically greater in the EV/DNG group than in the Microgynon group. When examining these symptoms during cycle days 1 - 21, a numerical reduction in the mean number of days with at least moderate pain or intensity of symptoms could be seen for most hormone related symptoms. For headache, the mean reduction was numerically greater in the EV/DNG group than in the Microgynon group (EV/DNG: mean ± SD -0.9 ± 3.0 days; Microgynon: -0.6 ± 3.0 days), while for pelvic pain (EV/DNG: mean ± SD -0.4 ± 2.1 days; Microgynon: -0.7 ± 2.5 days) and bloating or swelling (EV/DNG: mean ± SD 0.0 ± 2.0 days; Microgynon: -0.7 ± 2.5 days), it was numerically greater in the Microgynon than in the EV/DNG group.

- The pattern of bleeding or spotting episodes under treatment was similar in both groups; slight numerical differences in favor of EV/DNG were seen for a few parameters. Over the course of treatment, the percentage of subjects with withdrawal bleeding episodes was consistently numerically lower in the EV/DNG group (approximately 80% during cycles 1 - 5) than in the Microgynon group (around 90 - 95%). More subjects in the EV/DNG group (75 subjects) than in the Microgynon group (39 subjects) had any intracyclic bleeding episodes between cycles 2 and 6.

- Improvements compared to baseline could be seen for the PGWBI global score for both on-treatment time-points in both groups (admission cycle: EV/DNG mean 65.6% ± SD 8.3%, Microgynon 66.7% ± 8.0%; change from admission cycle to cycle 2: EV/DNG 2.0% ± 7.8%, Microgynon 1.1% ± 7.7%; change from admission cycle to cycle 5: EV/DNG 2.0% ± 8.0%, Microgynon 1.3% ± 8.6%), and for almost all individual PGWBI dimensions. Absolute improvements, as well as differences between treatment groups were small; considering the standard deviations, the results did not suggest a consistent trend towards more favourable results in one of the two treatment groups.

- The same was true for the Q-LES-Q results. For most on-treatment time-points in both groups, improvements compared to baseline could be seen. Absolute improvements, as well as differences between treatment groups were small. For the dimension "physical health", changes to baseline during cycle 2 (EV/DNG: mean 3.0% ± SD 15.3%, Microgynon: 1.6% ± 15.7%) and during cycle 5 (EV/DNG: mean 5.3% ± SD 17.8%, Microgynon: 2.9% ± 17.7%) were numerically slightly greater in the EV/DNG group than in the Microgynon group. Considering the standard deviations, the results for the other dimensions and items did not suggest a trend towards more favourable results in one of the two treatment groups.

- The number of subjects assessed by their investigators as either "much improved" or "very much improved" in the CGI assessment increased from cycle 2 to cycle 5 in both treatment groups. At both time-points, it was greater in the EV/DNG group than in the Microgynon group (cycle 2: EV/DNG: 83/204 [40.7%], Microgynon: 58/201 [28.9%]; cycle 5: EV/DNG: 113/187 [60.4%], Microgynon: 77/187 [41.2%]). Self-assessments by the subjects themselves were similar.

Results Summary — Safety

Safety results showed a pattern that could be expected for combined oral contraceptives (COCs). Numerical differences were seen for some adverse events; however with the exception of a few preferred terms, there was no consistent trend in favor of either treatment group. No notable differences between treatment groups were seen for other safety variables. These conclusions are based on the following findings:

- There were no deaths in this study. Nine (9) treatment-emergent serious adverse events (SAEs) were reported in this study, affecting 6/223 subjects (2.7%) in the EV/DNG group and 2/218 subjects (0.9%) in the Microgynon group. These comprised erysipelas, infectious mononucleosis (2 subjects), anaphylactic shock, and peritonsillar abscess in the EV/DNG group and ankle fracture and tonsillitis in the Microgynon group. Also included in the above numbers are muscle strain and pelvic fracture, which were recorded for one subject in the EV/DNG group. Although there was no record of any study drug intake, study drug was dispensed and not all was returned unused; thus it cannot be ruled out that this subject actually took study drug. None of these treatment-emergent SAEs was assessed as study drug related or led to discontinuation of the study drug; all SAEs were resolved at the end of the study.

- A total of 5 subjects in each group (EV/DNG group 2.2%, Microgynon group 2.3%) prematurely discontinued the study medication due to AEs.

- The overall incidence of treatment-emergent AEs (TEAEs) in the EV/DNG group (100/223 [44.8%]) was numerically lower than in the Microgynon group (117/218 [53.7%]). The overall incidence of gastrointestinal disorders was numerically lower in the EV/DNG group (EV/DNG: 29/223 [13.0%], Microgynon: 41/218 [18.8%]), while the overall incidence of infections and infestations (EV/DNG: 44/223 [19.7%], Microgynon: 36/218 [16.5%]), of nervous system disorders (EV/DNG: 40/223 [17.9%], Microgynon: 34/218 [15.6%]), and of reproductive system and breast disorders (EV/DNG: 51/223 [22.9%], Microgynon: 53/218 [24.3%]) was comparable between groups or even numerically slightly higher in the EV/DNG group.

- On the Medical Dictionary for Regulatory Activities (MedDRA) preferred term level, pelvic pain (EV/DNG: 37/223 [16.6%]; Microgynon: 35/218 [16.1%]) and headache (EV/DNG: 36/223 [16.1%]; Microgynon: 28/218 [12.8%]) were the most frequently reported preferred terms according to MedDRA. The incidence of abdominal distension (EV/DNG: 12/223 [5.4%]; Microgynon: 25/218 [11.5%]) was numerically higher in the Microgynon group than in the EV/DNG group.

- The incidence of TEAEs assessed by the investigators as study drug related was numerically higher on EV/DNG (14/223 [6.3%]) than on Microgynon (8/218 [3.7%]). On the preferred term level, considering the low incidences for most terms, there were no apparent differences between treatment groups except for headache, which was reported as study drug related for 6/223 EV/DNG subjects (2.7%) and for 1/218 Microgynon subjects (0.5%).

- Preferred terms reported with severe intensity for at least 1% of subjects in any group were headache, breast tenderness, abdominal distension, nausea, and pelvic pain. Although the absolute numbers of affected subjects were low, headache was reported with severe intensity for fewer subjects in the EV/DNG group (6/223 [2.7%]) than in the Microgynon group (10/218 [4.6%]). The same was true for nausea (EV/DNG: 2/223 [0.9%], Microgynon: 6/218 [2.8%]).

- In this study, no pregnancies were documented under treatment.

- There were no notable changes of systolic or diastolic blood pressure, heart rate, body weight, or BMI compared to baseline in any treatment group.

- At the final examination, 5/223 subjects in the EV/DNG group (2.2%) and 7/218 subjects in the Microgynon group (3.2%) had abnormal cervical smear results assessed as clinically relevant. Thus, the incidence of cervical smear results assessed as clinically relevant was numerically higher than at baseline (2 subjects in the EV/DNG group [0.9%]

and no subjects in the Microgynon group). Attempts were made to obtain follow-up information for all cases of cervical smear results assessed as clinically relevant that were ongoing at the end of the study. At the time of finalizing the study report, for 5 out of 12 cases either the investigator or the subjects had chosen against further follow-up; for the other 7 cases the investigators considered the event as resolved or as not clinically significant after further follow-up.

Conclusion(s)

EV/DNG met the primary endpoint and was shown to be superior to Microgynon with regard to the change in the average of the 3 highest VAS values of the hormone withdrawal associated symptoms, headache and pelvic pain, on cycle days 22 - 28 from baseline to cycle 6. Treatment with either COC improved the hormone withdrawal associated symptoms headache and pelvic pain, but the difference between the treatments was statistically significant in favor of EV/DNG. Data on the primary efficacy variable by country consistently showed a reduction of symptoms in both treatment groups. In women from Germany, France, Australia, and Finland the effect of EV/DNG was distinctly more pronounced.

Also, with regard to most of the secondary efficacy variables, EV/DNG was shown to be superior to Microgynon.

Both study drugs were well-tolerated and safety results were in line with those expected for COCs.

Publication(s):	None		
Date Created or Date Last Updated:	15 MAY 2012	Date of Clinical Study Report:	10 JAN 2012

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen, Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	ACRO c/- Pacific Medical Centre	36 Kildare Road	2148	Blacktown	AUSTRALIA
2	Burnside Clinical Trials Unit	141 Kensington Road	5065	Norwood	AUSTRALIA
3	Caringbah Medical and Dental Centre	Australian Clinical Research Organisation Level 2, 42 President Avenue	2229	Caringbah	AUSTRALIA
4	Family Planning Queensland	100 Alfred Street	4006	Fortitude Valley	AUSTRALIA
5	Jean Hailes Foundation for Womens Health	173 Carnish Road	3163	Clayton	AUSTRALIA
6	King Edward Memorial Hospital	University of WA School of Womens & Infant Health 374 Bagot Road	6008	Subiaco	AUSTRALIA

7	Peninsula Specialist Centre	Suite 4 Cnr George and Florence Streets	4021	Kipparing	AUSTRALIA
8	Queen Elizabeth II Medical Centre	Keogh Institute for Medical Research 3rd floor, A Block Verdun Street	6009	Nedlands	AUSTRALIA
9	Royal Hospital for Women	Barbara Gross Research Unit Barker Street Randwick	2031	Sydney	AUSTRALIA
10	Sydney Centre for Reproductive Health Reseach	Family Planning NSW 328-336 Liverpool Road	2031	Ashfield	AUSTRALIA
11	University of Adelaide	Level 6, Medical School Building Frome Road	5005	Adelaide	AUSTRALIA
12	Dextra Munkkivuoren Lääkärikeskus Oy	Raumantie 1a	00350	Helsinki	FINLAND
13	Lääkäriasema Cantti Oy	Hapelähteenkatu 40	70110	Kuopio	FINLAND
14	Lääkärikeskus Mehiläinen Töölö	Gyn-Research Laakarikeskus Mehilainen Pohjoinen Hesperiankatu 17 00260 Helsinki	00260	Helsinki	FINLAND
15	Laboratorio Simpanen	Tulliportinkatu 26 B	70100	Kuopio	FINLAND

16	Väestöliitto, Seksuaaliterveysklinikka, Helsinki	Seksuaaliterveysklinikka Kalevankatu 16	00100	Helsinki	FINLAND
17	Cabinet gynecologie	Cabinet gynecologie 5 rue des Louviers	78100	SAINT GERMAIN EN LAYE	FRANCE
18	Cabinet Médical Dr Honthaas, Cohen-Sourdille et De Reilhac	Cabinet Médical Dr Honthaas, Cohen-Sourdille et De Reilhac 3 pl Paul Emile Ladmirault	44000	NANTES	FRANCE
19	Cabinet médical Dr Patricia Rérolle	Cabinet médical Dr Patricia Rérolle 20 rue Daniel Stern	75015	PARIS	FRANCE
20	Cabinet Médical - Loiret - Olivet	Cabinet Médical 332, avenue du Loiret	45160	OLIVET	FRANCE
21	Cabinet Médical - Villersexel - Paris	Cabinet Médical 9 rue de Villersexel	75007	PARIS	FRANCE
22	Dr. Aliette Siboni-Frisch	Dr. Aliette Siboni-Frisch 72 boulevard de Strasbourg	31000	Toulouse	FRANCE
23	Dr Cecile Petrequin	34, rue du Ruisseau 75018 Paris	75018	Paris	FRANCE
24	Dr. Gwendoline Servan	Dr. Gwendoline Servan 6 rue Denave	69170	TARARE	FRANCE

25	Dr. Jocelyne Nataf-Maurin	Dr. Jocelyne Nataf-Maurin 9 boulevard Foch 83170 Brignoles	83170	Brignoles	FRANCE
26	Dr Matuchansky	11 avenue de LONGUEIL	78600	Maison Lafitte	FRANCE
27	Groupe Médical Ardaens Rohart Dewailly	Groupe Médical Ardaens Rohart Dewailly 1 rue Philippe de Girard	59113	SECLIN	FRANCE
28	Hôpital Mère et Enfants - CHU NANTES	CHU NANTES Service Gynécologie Obstétrique Hôpital Mere et Enfant 38 Bd Jean MONNET	44093	Nantes	FRANCE
29	Maternité Adolphe PINARD	10 rue du Dr Heydenreich service gynécologie	54042	Nancy	FRANCE
30	ClinPharm International GmbH	&Co KG Studienzentrum Schaeferstrasse 61	01067	Dresden	GERMANY
31	ClinPharm International GmbH and Co. KG	Studienzentrum Johannisplatz 1	04103	Leipzig	GERMANY
32	ClinPharm International GmbH&CoKG	Südring 23	44787	Bochum	GERMANY
33	Praxis Dr. S. Mucha & Dr. G. Schalk	Gemeinschaftspraxis Calvinstrasse 24	42103	Wuppertal	GERMANY
34	Praxis Hr. Dr. H. Gerlach	Willy-Brandt-Platz 4	45127	Essen	GERMANY
35	Praxis Hr. Dr. K. Greven	Pfarrstr. 47	30459	Hannover	GERMANY
36	Praxis Hr. Dr. S. Schönian	Rappenwörthstr. 48	76287	Rheinstetten	GERMANY

37	Praxis Hr. Dr. T. Gent	Im Alten Dorfe 23	22359	Hamburg	GERMANY
38	Praxis Hr. Dr. Werner Göttker-Schnetmann	Eschersheimer Landstr. 41	60322	Frankfurt	GERMANY
39	Praxis Hr. Prof. Dr. H.-J. Ahrendt	Halberstädter Strasse 122	39126	Magdeburg	GERMANY
40	Universitätsklinikum Schleswig-Holstein / AÖR	Campus Lübeck Klinik für Frauenheilkunde und Geburtshilfe Ratzeburger Allee 160	23538	Lübeck	GERMANY
41	Centro Médico Del Valle	Amores 942 Col. Del Valle	3100	Mexico, D.F.	MEXICO
42	Hospital Integral de la Mujer del Estado de Sonora	Reforma No. 355 Norte Col. Ley, 57.	83100	Hermosillo	MEXICO
43	Hospital Juárez de México SS	Av. Instituto Politécnico Nacional 5160 Col. Magdalena de las Salinas	07760	México, D.F.	MEXICO
44	Instituto Mexicano de Investigacion Clinica, SA de CV.	Durango 216 Col. Roma Delegación Cuauhtémoc	06700	Mexico	MEXICO
45	Nuevo Sanatorio Durango S.A. de C.V.	Durango 290 Col. Roma Delegación Cuauhtémoc	06700	Mexico	MEXICO
46	Centro de Salud Natahoyo-Tremañes	c/ Juan Carlos I s/n	33212	Gijón	SPAIN
47	Centro de Salud Petrer	c/ Jesús Zaragoza, nº 3	03610	Petrer	SPAIN

48	Centro de Salud Rincón de Loix	Av Juan Fuster Zaragoza Ed Aquarium III Bajo	03503	Benidorm	SPAIN
49	Clínica Diatros	c/ Aragó, 403-405 Escalera b, 2º3ª	08013	Barcelona	SPAIN
50	Gabinete Médico Velázquez	c/ Velázquez, 25 1º	28001	Madrid	SPAIN
51	Hospital del Mar	Servicio de Ginecología. Planta 5 Paseig Marítim, 25-29	08003	Barcelona	SPAIN
52	Inselspital Bern	Klinik für Frauenheilkunde Effingerstr. 102	3010	Bern	SWITZERLAND
53	Praxis Dr. Christoph Koenig	Gynaekologie/Geburtshilfe FMH Humboldt-Strasse 24	3013	Bern	SWITZERLAND
54	Universitätsspital Basel	Universitäts-Frauenklinik Spitalstrasse 21	4031	Basel	SWITZERLAND
55	Universitätsspital Zürich	Klinik für Gynäkologie Frauenklinikstrasse 10	8091	Zürich	SWITZERLAND
56	Chulalongkorn Hospital	Family Planning Clinic, King Chulalongkorn Memorial Hospital, 1873, Rama IV Road, Patumwan	10330	Bangkok	THAILAND
57	Ramathibodhi Hospital	Obsteric and Gynecology Department Ramathibodi Hospiatal.	10400	Bangkok	THAILAND

58	Siriraj Hospital, Mahidol	Siriraj Reproductive Health Research center, Department of Obstetrics and Gynecology, Faculty of Medicine 2 Prannok Road	10700	Bangkok	THAILAND
59	Bridge House Medical Centre	Bridge House Medical Centre MBChB, MRCGP, RCGP 11 Ladybridge Road Cheadle Hulme	SK8 5LL	Cheadle	UNITED KINGDOM
60	Castlemilk Health Centre	71 Dougrie Drive	G45 9AW	Glasgow	UNITED KINGDOM
61	Clarence Park Surgery	13 Clarence Road East Weston-super-Mare North Somerset BS23 4BP	BS23 4BP	Weston-super-Mare	UNITED KINGDOM
62	Greenwood and Sneinton Family Medical Centre	249 Sneinton Dale	NG2 4PJ	Nottingham	UNITED KINGDOM
63	MeDiNova Research	Mount Vernon Hospital Rickmansworth Road	HA6 2RN	Northwood	UNITED KINGDOM
64	Queen Charlottes & Chelseas Hospital	Department of Gynaecology Ground Floor Queen Charlotte's Hospital Du Cane Road	W12 0NN	London	UNITED KINGDOM

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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