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 Pharma AG/Bayer HealthCare AG	
Study Number:	90883 (304004)	NCT00185367
Study Phase:	III	
Official Study Title:	A multi-center, double-blind, double-dummy, controlled, randomized study to evaluate cycle control and safety of a four-phasic oral contraceptive containing estradiol valerate and dienogest (SH T00658ID) in comparison to an oral contraceptive containing ethinylestradiol and levonorgestrel (SH D 593 B) in healthy female volunteers aged between 18 and 50 years over 7 cycles.	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EV/DNG (Qlaira, BAY86-5027, SH T00658ID)	
Name of Active Ingredient:	Estradiol valerate (EV) and Dienogest (DNG)	
Dose and Mode of Administration:	1) Day 1 – 2: 3.0 mg EV; 2A) Day 3 – 7: 2.0 mg EV + 2.0 mg DNG; 2B) Day 8 – 24: 2.0 mg EV + 3.0 mg DNG; 3) Day 25 – 26: 1.0 mg EV; 4) Day 27 – 28: placebo; oral administration.	
Reference Therapy/Placebo		
Reference Therapy:	SH D 593 B (mono-phasic ethinylestradiol [EE] + levonorgestrel [LNG], Miranova) (Comparator).	
Dose and Mode of Administration:	Day 1 – 21: 0.02 mg EE + 0.10 mg LNG; Day 22 – 28: placebo; oral administration.	
Duration of Treatment:	Seven treatment cycles of 28 days each of Treatment or Comparator (no tablet-free interval).	
Studied period:	Date of first subjects' first visit:	02 MAR 2005
	Date of last subjects' last visit:	05 SEP 2006
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 01 (dated 06 JAN 2005) (valid only for Czech Republic) was enacted to meet the requirements of the Czech authorities.The eligibility of the subjects ≥45 years of age was to be tested also by mammography. For this reason, the CRFs of the Czech centers contained 5 inclusion criteria, the fifth one being: • Records of non-suspicious mammography obtained within 1 year before Visit 1 for women ≥45 years.	
Study Centre(s):	This study was conducted in Germany (19 centers), Czech Republic (5 centers), and France (10 centers).	
Methodology:	The study was performed as a multi-center, double-blind, double-dummy, controlled, randomized trial in fertile women aged between 18 and 50 years (inclusive; smokers not older than 30 years and with a daily cigarette consumption not exceeding 10). A total of 800 subjects seeking contraception were randomized into one of the two treatment arms (Treatment or Comparator) by stratifying the subjects	

	according to age groups (18 - 35 and 36 – 50 years), thus resulting in 4 randomization groups. To maintain blinding, a double dummy design was applied; each subject took 1 verum (test product or reference therapy) and 1 placebo tablet daily. The focus of investigation were the bleeding patterns and the cycle control of SH T00658ID (Treatment). The number of unintended pregnancies were calculated. Tablet intake and bleeding events were documented by the subjects on a daily basis in diary cards provided by the sponsor.
Indication/ Main Inclusion Criteria:	Indication: Oral contraception Main Inclusion criteria: Healthy female subjects, stratified into 2 age groups (18 to 35 years, and 36 to 50 years), smokers not older than 30 years and with a maximum of 10 cigarettes a day, seeking contraception
Study Objectives:	Overall: To evaluate bleeding patterns, cycle control, and safety of SH T00658ID in comparison to a reference oral contraceptive (OC) (SH D 593 B) containing 0.02 mg EE and 0.1 mg LNG. Primary: Bleeding pattern and cycle control Secondary: Number of unintended pregnancies; Subjective assessment of treatment by volunteer; Mean change in Psychological General Well-Being Index (PGWI); Change in McCoy Female Sexuality Questionnaire (MSFQ).
Evaluation Criteria:	Efficacy: Efficacy (Primary): Bleeding patterns and cycle control, including number of subjects with intracyclic bleeding within Cycles 2 to 7. Efficacy (Secondary): Number of unintended pregnancies Subjective assessment of treatment by subject Mean change in Psychological General Well-Being Index (PGWI) total score and subscale scores from baseline to treatment Cycles 4 and 7 Change in McCoy Female Sexuality Questionnaire (MFSQ) subscale scores from baseline to treatment Cycles 4 and 7 Safety: • Baseline findings • Adverse events (AEs) • Safety laboratory tests • Vital signs, including body weight, height, and body mass index (BMI) • Physical and gynecological examination, including breast palpation, transvaginal ultrasonography (TVU), and cytological cervical smear

Statistical Methods:	Efficacy: Descriptive statistics were used and no interim analyses were planned. Efficacy (Primary): Not applicable Efficacy (Secondary): Not applicable Safety: Descriptive statistics were used and no interim analyses were planned.
Number of Subjects:	Planned: 800 (400 per treatment group; 200 per age stratum) Analyzed: 798 (399 per treatment group; 198 to 201 per age stratum) (full analysis set [FAS])

Study Results

Results Summary — Subject Disposition and Baseline

The initial screening pool consisted of 846 subjects, 42 of whom were not randomized. Of the 804 randomized subjects (402 *per* treatment group), 6 did not receive any study medication and were assigned therefore to the listing-only set (LOS) (3 *per* treatment group). Thus, the FAS resulted in 798 subjects (399 *per* treatment group). The age strata were very well matched within each treatment group (Treatment: 199 subjects for the age stratum 18 to 35 years, 200 for the age stratum 36 to 50 years; Comparator: 201 and 198, respectively). Forty-four subjects prematurely discontinued the study (21 for Treatment and 23 for Comparator). The proportion of drop-outs due to AEs was balanced (3.3% of FAS in each treatment group). After evaluation of the major protocol deviations, the per-protocol set per-protocol set (PPS) consisted of 727 subjects (365 for Treatment [91.5% of FAS] and 362 for Comparator [90.7% of FAS]).

Within each treatment group and across the age strata, the baseline and gynecological/clinical characteristics (including medical history and baseline findings) were well balanced. Nearly all subjects were Caucasian, with the exception of one Black and one Asian. The occurrence of intracyclic bleeding in the 6 months preceding the study was also balanced (3.0% for Treatment and 2.0% for Comparator).

The overall treatment compliance was good and comparable between Treatment and Comparator (97.1% and 96.8% of the planned tablet intake, respectively).

Results Summary — Efficacy

Note: Unless otherwise specified, the results refer to FAS analyses. Also, the results refer to the overall treatment groups (18 – 50 years), unless the age strata are specifically mentioned (younger age stratum: 18 – 35 years; older age stratum: 36 – 50 years).

Bleeding patterns and cycle control:

A) Bleeding patterns (analyses by reference period)

Number of bleeding/spotting days:

- Overall, exposure to Treatment led to fewer days with bleeding/spotting than exposure to Comparator (Reference Period 1: 17.3 ± 10.4 days [95% confidence interval (CI): 16.3 to 18.3 days] versus 21.5 ± 8.6 days [CI: 20.6 to 22.3 days] [Reference Period 1 contains also the initial bleeding episode that triggered the first intake of study medication (in

other words, the first treatment cycle included two bleeding episodes because for switchers and new starters the first day of tablet intake was the first day of withdrawal or menstrual bleeding of the preceding cycle, respectively)]; Reference Period 2: 13.4 ± 9.3 days [CI: 12.4 to 14.3 days] versus 15.9 ± 7.1 days [CI: 15.2 to 16.6 days]).
- The younger age stratum tended to bleed slightly longer than the older age stratum (for Treatment in Reference Period 1, for example, 18.5 ± 10.6 days in the younger age stratum versus 16.2 ± 10.1 days in the older age stratum). This age-dependent effect, however, was observed also under Comparator. At any rate, the age-related differences became less evident in Reference Period 2.
- FAS and PPS analyses yielded similar results.

Number of bleeding/spotting episodes:

- In Reference Period 1, the mean number of episodes was slightly lower under Treatment (3.7 ± 1.4) than under Comparator (4.1 ± 0.9).
- The differences between Treatment and Comparator were slightly more evident in the older age stratum (Treatment: 3.6 ± 1.4; Comparator: 4.1 ± 1.0) than in the younger age stratum (Treatment: 3.9 ± 1.4; Comparator: 4.1 ± 0.9).
- In Reference Period 2, the number of episodes decreased in both treatment groups (Treatment: 3.0 ± 1.3; Comparator: 3.1 ± 0.9).
- FAS and PPS analyses yielded similar results.

Mean length of bleeding/spotting episodes:

- The mean length of bleeding/spotting episodes was slightly lower under Treatment than under Comparator (in Reference Period 1, for example, 4.6 ± 2.6 versus 5.2 ± 2.0 days; in Reference Period 2, 4.5 ± 2.6 versus 5.1 ± 1.8 days).
- The shorter duration of the episodes seemed independent of age stratum.
- FAS and PPS analyses yielded similar results.

Maximum length of bleeding/spotting episodes:

- The maximum length of bleeding/spotting episodes was slightly lower under Treatment than under Comparator (6.5 ± 3.9 versus 7.2 ± 3.9 days in Reference Period 1; 5.9 ± 4.1 versus 6.4 ± 3.0 days in Reference Period 2).
- This effect seemed independent of age stratum.
- FAS and PPS analyses yielded similar results.

Range of length of bleeding/spotting episodes:

- For Treatment, the range of length went from 3.4 ± 3.5 days in Reference Period 1 to 2.7 ± 3.5 days in Reference Period 2. For Comparator, similarly, the range of length went from 3.9 ± 3.7 days in Reference Period 1 to 2.4 ± 2.9 days in Reference Period 2.
- This trend was observed also across age strata.
- There were no evident differences between FAS and PPS.

Number of spotting-only days:

- In Reference Period 1, the mean number of spotting-only days was comparable between treatments (Treatment: 7.3 ± 7.8 days; Comparator: 7.3 ± 6.4 days).
- In Reference Period 2, the mean number of spotting-only days was higher for Treatment than for Comparator (6.3 ± 7.1 versus 5.5 ± 5.4 days, respectively), although the medians were comparable (5 days).
- In the Treatment group, younger subjects had more spotting-only days than older subjects, at least in Reference Period 1 (younger stratum: 8.0 ± 8.9 days; older stratum: 6.6 ± 6.5 days), although this was not reflected in the medians (5.0 and 6.0 days, respectively).
- FAS and PPS analyses yielded similar results.

Number of spotting-only episodes:

- In both reference periods, the mean number of spotting-only episodes was slightly higher for Treatment (0.9 ± 1.2 in Reference Period 1; 0.8 ± 1.2 in Reference Period 2) than for Comparator (0.6 ± 1.0 in Reference Period 1; 0.4 ± 0.9 in Reference Period 2), although the medians were comparable in Reference Period 2 (0.0), irrespective of treatment and age.
- FAS and PPS analyses yielded similar results.

Mean length of spotting-only episodes:

- This parameter seemed comparable for Treatment (Reference Period 1: 2.9 ± 2.0 days; Reference Period 2: 3.0 ± 1.6 days) and Comparator (Reference Period 1: 2.6 ± 1.7 days; Reference Period 2: 3.1 ± 2.6 days), given a certain variability across age strata and between reference periods.
- FAS and PPS analyses yielded similar results.

Maximum length of spotting-only episodes:

- This parameter seemed comparable in both reference periods and across age strata (median of 3 days in nearly all cases, with the exception of the older age stratum of Comparator [median: 2 days]).
- FAS and PPS analyses yielded similar results.

Range of length of spotting-only episodes:

- For Treatment, there were hardly any differences between Reference Periods 1 and 2 (1.1 ± 2.0 and 1.1 ± 2.6 days, respectively). The same was true for Comparator (0.9 ± 1.8 and 0.9 ± 2.3 days, respectively), although the means were slightly lower than for Treatment.
- At any rate, the medians were 0 days for Treatment and Comparator, including reference periods and age strata.
- There were no evident differences between FAS and PPS.

B) Cycle control (analyses by cycle)

Withdrawal bleeding

Frequency of subjects with and without withdrawal bleeding:

- Through the cycles, subjects with withdrawal bleeding were less frequent under Treatment than under Comparator (range for Treatment: 77.7% to 83.2%; range for Comparator: 89.5% to 93.8%). In other words, absence of withdrawal bleeding was more frequent under Treatment (range: 16.8% to 22.3%) than under Comparator (range: 6.2% to 10.5%).
- This Treatment effect was slightly more pronounced in the older age stratum (range: 16.0% to 24.4%) than in the younger age stratum (range: 12.5% to 20.3%).
- FAS and PPS analyses yielded similar results.

Length of withdrawal bleeding episodes:

- Through the cycles, mean and median lengths of withdrawal bleeding were slightly lower for Treatment (median: 4 days) than for Comparator (median: 5 days).
- The differences between Treatment and Comparator were slightly more pronounced in the younger age stratum (Cycle 4, for example, Treatment: 4.4 ± 2.4 days; Comparator: 5.2 ± 1.7 days).
- FAS and PPS analyses yielded similar results.

Maximum intensity of withdrawal bleeding episodes:

- Through the cycles, this parameter was on average lower for Treatment (median score: 3 [light bleeding]) than for Comparator (median score: 4 [normal bleeding]).
- There were no evident age-dependent effects.
- FAS and PPS analyses yielded similar results.

Frequency of subjects by given intensity scores (spotting, light, normal, or heavy bleeding):

- Through the cycles, the relative proportion of subjects with spotting and light bleeding was more pronounced under Treatment than under Comparator.
- FAS and PPS analyses yielded similar results.

Onset of withdrawal bleeding episodes (for Treatment the onset of withdrawal bleeding was calculated from the end of the exposure to the progestogen component [Day 24] [Days 25 and 26 delivered only EV]. In other words, the count for the onset started on Day 25 of each cycle. For Comparator, the count started on Day 22 [first day of placebo]):

- The mean onset of withdrawal bleeding was slightly longer under Treatment (range through the cycles: 3.0 ± 4.1 to 4.7 ± 6.1 days) than under Comparator (range: 2.7 ± 3.0 to 3.8 ± 5.2 days), although this was not reflected in the median onset (Treatment: mostly 2 days; Comparator: 3 days in all cycles).
- Within the Treatment group, the younger age stratum showed a slightly higher variability through the cycles than the older age stratum.
- FAS and PPS analyses yielded similar results.

Intracyclic bleeding

Frequency of subjects with intracyclic bleeding:

- In Cycles 1 and 2, intracyclic bleeding was more frequent under Treatment than under Comparator (in Cycle 2, for example, 16.4% versus 11.8%).
- From Cycle 5, there were hardly differences anymore between Treatment (from 10.7% to 12.9%) and Comparator (approximately 10%).
- In the younger age stratum, the differences between Treatment and Comparator were more evident than in the older age stratum.
- FAS and PPS analyses yielded similar results.

Number of intracyclic bleeding episodes:

- There were hardly any differences between Treatment (between 0.1 and 0.2 episodes through the cycles) and Comparator (mostly 0.1 episodes).
- FAS and PPS analyses yielded similar results.

Maximum length of intracyclic bleeding episodes:

- There was a certain by-cycle variability for this parameter, thus some differences between Treatment and Comparator were probably irrelevant.
- FAS and PPS analyses yielded similar results.

Number of days with intracyclic bleeding:

- There was a certain by-cycle variability for this parameter, thus some differences between Treatment and Comparator were probably irrelevant (given that the medians were 0.0 in all cycles and across all strata).
- FAS and PPS analyses yielded similar results.

Maximum intensity of intracyclic bleeding episodes:

- Treatment was associated with a lighter bleeding intensity (spotting and light bleeding)

than Comparator.
- FAS and PPS analyses yielded similar results.

Frequency of subjects with at least 1 intracyclic bleeding:
- Considering Cycles 2 to 7, intracyclic bleeding was more frequent under Treatment than under Comparator (41.9% versus 36.2%).
- The differences between Treatment and Comparator were almost completely attributable to the younger age stratum (47.4% versus 36.7%), whereas in the older age stratum Treatment and Comparator showed similar frequencies (36.5% and 35.8%, respectively).
- FAS and PPS analyses yielded similar results.

In summary, the total number of bleeding days (bleeding + spotting) was on average lower under Treatment than under Comparator. Also, the bleeding observed under Treatment was less intense. Thus, although intracyclic bleeding was slightly more frequent under Treatment, this was not associated with a heavier bleeding intensity altogether.

Unintended pregnancies:

Seven pregnancies were recorded altogether in the course of the study, only 1 of which occurred during the treatment phase. This occurred in the Comparator group and was assessed as due to method failure.

Subjective assessment of subject:

In terms of overall satisfaction (very or somewhat satisfied, neither satisfied or dissatisfied, dissatisfied, very dissatisfied), the proportion of very satisfied subjects was slightly higher for Treatment (39.8% of FAS) than for Comparator (35.3%). There were no age-related effects.

In terms of overall emotional well-being (much or somewhat better, same, somewhat or much worse), a somewhat better overall emotional well-being was slightly more frequent for Treatment (13.8%, versus 11.8% for Comparator), particularly in the younger age stratum (15.1% versus 10.4%).

In terms of overall physical well-being (much or somewhat better, same, much or somewhat worse), a somewhat better overall physical well-being was slightly more frequent for Treatment than for Comparator (14.3% versus 11.3%, respectively), particularly in the younger age stratum (16.1% versus 10.0%, respectively).

In terms of choice of contraceptive method, similar proportions of subjects intended to continue Treatment (52.9%) or Comparator (52.1%), whereas the older age stratum had a slight preference for Treatment (57.0%) compared to Comparator (54.5%).

Psychological General Well-Being Index (PGWBI):

In terms of global score and subscales anxiety, depressed mood, positive well-being, self-control, general health, and vitality there were no differences between Treatment and Comparator; there were no evident changes between Baseline and Cycle 4 or Final Visit.

McCoy Female Sexuality Questionnaire (MFSQ):

Total score: The total MFSQ score (higher MFSQ scores indicated a better sexual function) remained stable through the visits for both treatments (Final Visit: 59.6 ± 18.7 for Treatment and 59.7 ± 19.2 for Comparator; Baseline: 59.8 ± 17.7 and 61.4 ± 18.1, respectively). The results were comparable across age strata.

Subscale sexual interest: This subscore remained stable through the visits in both treatment groups (Final Visit: 18.1 ± 5.0 for Treatment and 18.3 ± 5.0 for Comparator; Baseline: 18.5 ± 5.0 and 18.6 ± 5.1, respectively). The results were comparable across age strata.

Subscale satisfaction with frequency of sexual activity: This subscore remained fairly stable through the visits in both treatment groups (Final Visit: 16.6 ± 10.9 for Treatment and 17.1 ± 10.3 for Comparator; Baseline: 16.5 ± 8.6 and 17.6 ± 10.5, respectively). The results were comparable across age strata.

Subscale vaginal lubrication: This subscore remained stable through the visits in both treatment groups (Final Visit: 15.5 ± 4.8 for Treatment and 15.1 ± 4.7 for Comparator; Baseline: 15.3 ± 4.9 and 15.3 ± 4.6, respectively). The results were comparable across age strata.

Subscale attractiveness: This subscore remained stable through the visits in both treatment groups (Final Visit: 10.1 ± 2.3 for Treatment and 10.0 ± 2.5 for Comparator; Baseline: 10.2 ± 2.4 and 10.2 ± 2.4, respectively). The results were comparable across age strata.

The above FAS analyses were all confirmed by the corresponding PPS analyses.

Results Summary — Safety

Baseline findings:

In the FAS, the overall frequency of baseline findings was comparable in the two treatment groups (Treatment: 15.0%; Comparator: 14.8%). In both treatment groups, the older age stratum was over-proportionally affected (20.0% and 16.2%, respectively) than the younger age stratum (10.1% and 13.4%, respectively). Two baseline findings were rated as serious in 2 screening failures (listing-only set) (Abortion spontaneous and Trisomy 21 [of fetus]) (MedDRA Preferred Terms, Version 9.0).

Adverse events:

A total of 338 AEs were recorded in the study, 176 for Treatment (affecting 108 subjects, or 27.1% of FAS) and 162 for Comparator (affecting 102 subjects, or 25.6% of FAS). In the younger age stratum (18 to 35 years) the frequency of affected subjects was comparable between treatments (27.1% for Treatment and 26.9% for Comparator). In the older age stratum (36 to 50 years) the frequency of affected subjects was slightly higher for Treatment (27.0%) than for Comparator (24.2%).

There were no deaths.

Eight of the 338 AEs were rated as serious, 5 in the Treatment group (affecting 4 subjects, or 1.0% of FAS) and 3 in the Comparator group (affecting 3 subjects, or 0.8% of FAS). An age-specific pattern of serious sdverse events (SAEs) was not evident.

The 5 SAEs recorded under Treatment were:

- Ovarian cyst ruptured (investigator: unlikely related; Sponsor: possibly related)
- Autonomic nervous system imbalance (concomitant SAE in the same subject with ovarian cyst ruptured and rated as a secondary symptom of ovarian cyst ruptured and not as an SAE per se)
- Vulval abscess (unrelated)
- Chronic tonsillitis (unrelated)
- Renal colic (unrelated)

The 3 SAEs recorded under Comparator were:

- Breast cancer (rated as unlikely related by the investigator but as possibly related by the Sponsor)
- Cholelithiasis (unlikely related)
- Intervertebral disc protrusion (unrelated) (all MedDRA Preferred Terms, Version 9.0)

Drug discontinuations due to AEs (AE withdrawals for brevity) were limited and balanced (3.3% of FAS in both treatment groups). In the Treatment group, AE withdrawals were slightly over-proportional in the younger age stratum (5.0%) compared to the older age stratum (1.5%); in the Comparator group there were hardly any differences between younger and older strata (3.5% and 3.0%, respectively). In terms of type of AE withdrawals, a pattern could not be recognized in the case of Treatment (low-frequency single events [0.3%]). In the case of Comparator, in turn, Acne accounted for 1.0% of the AE withdrawals (4 cases); Migraine and Weight increase for 0.8% (3 cases, respectively); and Headache for 0.5% (2 cases).

In terms of overall AE frequency by Primary MedDRA System Organ Class (SOC), there were no imbalances between the treatment groups, if not for slight differences in the SOCs Infections and infestations (12.8% for Treatment; 9.3% for Comparator) and Reproductive system and breast disorders (6.3% for Treatment; 4.0% for Comparator). For the SOC Infections and infestations, the differences were slightly more pronounced in the younger age stratum (15.6% for Treatment versus 10.0% for Comparator), partly explained by a higher frequency of Vaginal infection in this stratum (Treatment: 4.0%; Comparator: 0.5%). For the SOC Reproductive system and breast disorders, the slight imbalance was due to a slightly higher incidence of Breast pain in the Treatment group (3.8%, versus 1.3% in the Comparator group). In addition, the frequency of Breast pain was slightly over-proportional in the older age stratum (Treatment: 6.0%; Comparator: 2.0%). At any rate, Breast pain was a reason for discontinuation only in 1 case for Treatment and in 1 case for Comparator.

Through the MedDRA SOCs, besides the case of Breast cancer in the Comparator group (already described among the SAEs), other AEs of gynecological/special interest were observed at low or sporadic frequency, for example Ovarian cyst (Treatment: 0.8%; Comparator: 1.0%); Fibroadenoma of breast (Treatment: 0.3%; Comparator: 0.0%); Uterine leiomyoma (Treatment: 0.0%; Comparator: 0.3%); Smear cervix abnormal (Treatment: 0.3%; Comparator: 0.8%); Cervical dysplasia (Treatment: 0.3%; Comparator: 0.0%); Tachycardia (Treatment: 0.3%; Comparator: 0.0%); Thrombophlebitis superficial (Treatment: 0.0%; Comparator: 0.3%); Varicose vein (Treatment: 0.0%; Comparator: 0.3%); Migraine with aura (Treatment: 0.3%; Comparator: 0.0%). Some cases of mood alteration (including Depression and Depressed mood) were also observed, summing up to balanced frequencies between Treatment and Comparator. There were no cases of venous or arterial thromboembolism.

In general, the most frequent AEs (≥1% of FAS) occurring under Treatment were:

- Breast pain (3.8%)
- Headache (2.5%)
- Vaginal infection (2.5%)
- Cystitis (2.0%).

The most frequent AEs under Comparator were:

- Acne (3.3%)
- Headache (3.3%)
- Nasopharyngitis (1.8%)
- Migraine (1.5%)

Thus, the pattern of most frequent AEs was slightly different between the two treatments.

The patterns of most frequent AEs differed also in terms of age stratum. For Treatment, for example, the most frequent AEs in the younger age stratum were:

- Vaginal infection (4.0%)
- Cystitis (3.0%)
- Acne (2.0%)

For Comparator, these were:

- Acne (4.5%)
- Headache (2.0%)

In the older age stratum, in turn, Breast pain (6.0%) and Headache (4.0%) prevailed in the Treatment group, whereas Headache (4.5%) and Nasopharyngitis (2.5%) prevailed in the Comparator group.

The most frequent adverse drug reactions (ADRs; or AEs at least possibly related to the study medication) under Treatment were:

- Breast pain (3.3%)
- Headache (1.8%)
- Acne (1.3%)
- Alopecia (0.8%)

For Comparator, the most frequent ADRs were:

- Acne (2.3%)
- Headache (1.8%)
- Migraine (1.3%)
- Alopecia (1.0%)
- Breast pain (1.0%)
- Weight increased (1.0%).

Thus, Treatment was associated with fewer common ADRs (≥1% of subjects) than Comparator. The pattern of ADRs was also different, with Breast pain emerging as most common ADR of Treatment and Acne as most common ADR of Comparator.

An age-specific pattern was observed also for the ADRs. In the younger age stratum, Acne was the most frequent ADR in both treatment groups (Treatment: 2.0%; Comparator: 3.5%). In the older age stratum, Breast pain was the most frequent ADR under Treatment (5.5%), whereas Headache was the most frequent ADR under Comparator (2.5%).

In general, the frequency of subjects with ADRs was only slightly higher under Treatment (10.0%) than under Comparator (8.5%). A similar pattern was observed in the younger age stratum (Treatment: 9.5%; Comparator: 8.5%) and in the older age stratum (Treatment: 10.5%; Comparator: 8.6%).

Noticeable imbalances between the two treatment groups were not present for any of the AE characteristics (intensity, pattern, and so on). In particular, there were no cases with fatal outcome.

Concomitant drug treatment was required in a slightly higher proportion of subjects in the Treatment group (19.3%) than in the Comparator group (16.3%).

A recovered/resolved outcome was documented in 25.8% of the subjects in the Treatment

group and in 24.1% of the subjects in the Comparator group. The AEs recovering/resolving were balanced (0.5% in each treatment group). Not recovered/not resolved AEs were present in 1.5% of the Treatment group and in 2.3% of the Comparator group. There was only 1 AE with outcome recovered/resolved with residual effects (1 case of Herpes simplex in the Treatment group).

Safety laboratory tests:

The results of the safety laboratory tests were unremarkable for most of the parameters, i.e., the mean values remained within normal range at Final Visit (Final Visit was planned within 14 days after end of treatment) in both treatment groups and across age strata. The frequency of individual abnormalities was mostly balanced between the two treatments. Shift analyses showed mostly no systematic changes, or, when changes were present, there were hardly any differences between the two treatments. Clinically-significant laboratory abnormalities, in turn, were slightly more frequent under Comparator.

In particular, in terms of blood lipids, Treatment was similar to Comparator in inducing a slight reduction of mean levels of total cholesterol (particularly in the younger age stratum), in maintaining stable triglyceride levels, and in inducing a slight reduction of LDL-cholesterol. These positive effects were paralleled by a slight, similar reduction of HDL-cholesterol in the two treatment groups.

In terms of liver enzymes, Treatment and Comparator were similar in inducing minor elevations of the mean levels of alkaline phosphatase, gamma-GT, and ALAT, whereas the mean levels of cholinesterase were slightly reduced in both groups. Also, Treatment was characterized by fewer cases of clinically-relevant increases of liver enzymes (2 cases) compared to Comparator (4 cases).

In terms of HbA1C (a retrospective index of glucose control over time), Treatment and Comparator did not induce any changes of the mean levels of HbA1C and did not increase the frequency of subjects with abnormal HbA1C.

Vital signs:

Blood pressure: The mean blood pressure levels (both systolic and diastolic) remained normal and stable through the study visits. This was true for both treatment groups and across age strata. The proportion of subjects with abnormal blood pressure (systolic >140 mmHg; diastolic >90 mmHg) was limited and observed only in the Comparator group, especially in the older age stratum. The mean absolute individual changes from Baseline were minimal in both groups and across age strata.

Heart rate: The heart rate was stable through the study visits, regardless of treatment and age stratum.

Body weight: The mean body weight remained stable in both treatment groups and across age strata. On average, at Screening the older age stratum was slightly heavier than the younger age stratum, however the mean weight did not increase at Final Visit.

Body mass index (BMI): The mean BMI remained stable at Final Visit compared to Screening, although the older age stratum showed a slightly higher BMI than the younger age stratum. On average, the individual absolute changes were minimal. The transitions from higher to lower BMI were at least as numerous as the transitions from lower to higher BMI.

Physical examination and gynecological examination (including breast palpation, TVU, and cervical smear):

Physical examination: All abnormal findings were documented as baseline findings if observed at Screening and as AEs if observed at Final Visit, therefore they are included in the baseline-finding and AE analyses.

Gynecological examination (including breast palpation and TVU): All abnormal findings were documented as baseline findings if observed at Screening and as AEs if observed at Final Visit, therefore they are included in the baseline-finding and AE analyses.

Cervical smear: Abnormal findings at Final Visit were limited and balanced between the treatment groups. These cases consisted of a Pap IVa and a Pap III in the Treatment group; and of 2 cases of Pap III D and 1 case of Pap IVa in the Comparator group. All cases were documented as AEs; they were reported as unrelated to the study medication and were recovered/resolved at the end of the study.

Back-up contraception:

Back-up contraception was used by a very low percentage of subjects through the treatment cycles, consisting mostly of condoms (range of frequency: Treatment: 0.3% to 1.3%; Comparator: 0.5% to 2.5%).

Previous and concomitant medication:

Previous use of medication was reported by similar numbers of subjects in the two treatment groups (96.0% and 95.5%, respectively), without evident age-related differences. Imbalances in the use of given classes of medication were not evident.

Use of concomitant or follow-up medication was documented in equal percentages of subjects (87.7%) (concomitant medication included also medication started after termination of treatment with the study medications [follow-up medication]) in the two treatment groups (given that concomitant medication due to AEs was reported in 19.3% of the subjects exposed to Treatment and in 16.3% of the subjects exposed to Comparator). Within the Comparator group, there was a slight disproportion of intake of concomitant medication, i.e., slightly less than average in the younger age stratum (84.1%) and slightly more than average in the older age stratum (91.4%), whereas in the Treatment group there were hardly age-related differences (younger stratum: 88.9%; older stratum: 86.5%). In terms of type of medication, differences between groups or across age strata were limited.

Conclusion(s)

The main focus of the present study was to compare the bleeding patterns and cycle control of a four-phasic, sequential preparation of combined oral contraceptive (estradiol valerate [EV] + dienogest [DNG]), to those of a low-dose monophasic preparation marketed for oral contraception (0.020 mg ethinylestradiol [EE] + 0.100 mg levonorgestrel [LNG]; Miranova).

In this study of 798 subjects, the total number of bleeding days (bleeding + spotting) *per* reference period was on average lower under EV + DNG than under low-dose EE + LNG. Also, the bleeding events (both scheduled and unscheduled) were less intense under EV + DNG (relative predominance of spotting and light bleeding) than under EE + LNG (relative predominance of normal bleeding). Thus, although intracyclic bleeding was slightly more frequent under EV + DNG, this was not associated with a heavier bleeding intensity altogether.

The overall reduction of bleeding observed with EV + DNG was also reflected in the reduction of frequency and intensity of withdrawal bleeding. A noticeable feature of four-phasic EV + DNG, therefore, was a frequent absence of withdrawal bleeding (experienced through the cycles by 16.8% to 22.3% of the subjects exposed to EV + DNG, *versus* 6.2% to 10.5% of the subjects exposed to low-dose EE + LNG). Upon EV + DNG, the absence of withdrawal bleeding was relatively more frequent in the older age stratum (36 to 50 years) (16.0% to 24.4%) than in the younger age stratum (18 to 35 years) (12.5% to 20.3%).

Treatment with EV + DNG for 7 treatment cycles did not result in any unintended pregnancies.

All assessments of general, psychological, and sexual well-being concurred to indicate that EV + DNG is at least as favorable as the low-dose preparation EE + LNG.

The safety profile of EV + DNG was mostly comparable to that of EE + LNG. The only serious AE rated as related to EV + DNG was a case of Ovarian cyst ruptured.

Common ADRs (≥1% of exposed subjects) under EV + DNG were Breast pain (3.3%), Headache (1.8%), and Acne (1.3%). The ADRs observed under EV + DNG differed in ranking and type from those documented under low-dose EE + LNG (Acne [2.3%]; Headache [1.8%]; Migraine [1.3%]; Alopecia [1.0%]; Breast pain [1.0%]; and Weight increase [1.0%]).

In the present study, exposure to EV + DNG was not associated with any venous or arterial thromboembolism or with other severe, low-frequency side effects of combined oral contraceptives.

Publication(s):	Ahrendt HJ, Makalová D, Parke S, Mellinger U, Mansour D. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. Contraception. 2009 Nov;80(5):436-44.		
Date Created or Date Last Updated:	25 APR 2012	Date of Clinical Study Report:	05 APR 2007

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	Femina Sana s.r.o	Perlitkova 1825/11 Provozovna Konevova 2495/221	13000	Praha	CZECH REPUBLIC
2	Provozorna Gynekologicka ordinace Dr. Tesar	Ohmova 271	109 00	Praha 10	CZECH REPUBLIC
3	Soukroma gynekologicka ambulance	private practice Dolni 101	70400	Ostrava - Zabreh	CZECH REPUBLIC
4	Soukroma gynekologicka ambulance	Soukroma gynekologicka ambulance Zdrav. zarizeni Slovany Tr. Francouzska 4 307 08 Plzen	30708	Plzen	CZECH REPUBLIC
5	Soukroma gynekologicka ambulance	Private practice Palackeho 313	74245	Fulnek	CZECH REPUBLIC
6	Cabinet medical	4, place centrale 21800 Quetigny	21800	Quetigny	FRANCE

7	Centre Hospitalier de l Estuaire	Centre Hospitalier de l Estuaire Service de Gynecologie Chemin de la Plane	14601	Honfleur	FRANCE
8	Centre Medical du Val de Loire	Centre Medical du Val de Loire 49 boulevard Jerome Tresaguet 58000 Nevers	58000	Nevers	FRANCE
9	Clinique d Occitanie	Clinique d Occitanie 20 avenue Bernard IV 31600 Muret	31600	Muret	FRANCE
10	Dr. Aliette Siboni-Frisch	Dr. Aliette Siboni-Frisch 72 boulevard de Strasbourg	31000	Toulouse	FRANCE
11	Dr. Anne-Isabelle Richet	Dr. Anne-Isabelle Richet 109 rue de l Universite 75007 Paris	75007	Paris	FRANCE
12	Dr. Annette Mercier	Dr. Annette Mercier 18 place Charles de Gaulle 29600 Morlaix	29600	Morlaix	FRANCE
13	Dr. Gwendoline Servan	Dr. Gwendoline Servan 6 rue Denave	69170	TARARE	FRANCE

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18	Frauenarztpraxis Dr. Buchberger	Frauenarztpraxis Hauptstrasse 17a	85579	Neubiberg	GERMANY
19	Frauenarztpraxis Dr. Wetzel	Helsunger Str. 7	38889	Blankenburg	GERMANY
20	Frauenarztpraxis Hr. Dr. B. Hamann	Wollankstrasse 11	13187	Berlin	GERMANY
21	Frauenarztpraxis Hr. Dr. H. Lindecke	Frankfurter Allee 54	10247	Berlin	GERMANY
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23	Praxis Fr. C. Burgkhardt	Frauenarztpraxis Gletschersteinstrasse 34	04299	Leipzig	GERMANY
24	Praxis Fr. Dr. A. Braune	Frauenarztpraxis Domplatz 11	39104	Magdeburg	GERMANY
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26	Praxis Fr. Dr. A. Münzberger	Frauenarztpraxis Kirchgasse 5	04720	Döbeln	GERMANY
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32	Praxis Hr. Dr. U. Kopprasch	Frauenarztpraxis Amalie-Dietrich-Platz 5	01169	Dresden	GERMANY
33	Praxis Hr. Prof. Dr. H.-J. Ahrendt	Halberstädter Strasse 122	39126	Magdeburg	GERMANY
34	Praxis Hr. R. Wähnert	Frauenarztpraxis Leipziger Str. 22	07545	Gera	GERMANY

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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