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:	91554	NCT00914693
Study Phase:	III	
Official Study Title:	Multi-center, open-label, uncontrolled study to investigate the efficacy and safety of the transdermal contraceptive patch containing 0.55 mg ethinyl estradiol and 2.1 mg gestodene (material no. 80876395) in a 21-day regimen for 13 cycles in 1650 healthy female subjects.	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EE/GSD (BAY 86-5016) Transdermal Contraceptive Patch [material no. 80876395]	
Name of Active Ingredient:	Ethinyl estradiol (EE) and gestodene (GSD)	
Dose and Mode of Administration:	0.55 mg of EE per patch, daily delivery rate of approximately 8 µg EE (equivalent to approximately 18 µg per oral); 2.1 mg GSD per patch, daily delivery rate of approximately 55 µg GSD (equivalent to approximately 55 µg per oral) Mode of administration: Transdermal	
Reference Therapy/Placebo		
Reference Therapy:	None	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	21-day regimen per cycle (1 patch a week for 3 weeks followed by a 7-day patch-free interval) for 13 treatment cycles.	
Studied period:	Date of first subjects' first visit:	21 APR 2009
	Date of last subjects' last visit:	20 SEP 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	This study was conducted at 60 study centers in 7 countries: 5 centers in Australia, 5 centers in Chile, 7 centers in France, 17 centers in Germany, 11 centers in Italy, 5 centers in Mexico, and 10 centers in Spain.	
Methodology:	The study comprised a screening visit, an admission visit, 3 treatment visits, and a final visit.	

	Only one patch was worn at a time. Each patch was used as follows so that the 3 patches and the 7-day patch-free interval composed a 28-day cycle: 1st patch Day 1: application of the first patch 2nd patch Day 8: removal of the first patch and immediate application of the second patch 3rd patch Day 15: removal of the second patch and immediate application of the third patch No patch Day 22: removal of the third patch (no patch during days 22 - 28). Patch removal was to occur on the same day of the week and at the same time of day that the first patch was applied ("Patch Change Day"). Subsequent cycles were to start on the same Patch Change Day, after the 7-day patch-free interval (Days 22 - 28). Withdrawal bleeding usually occurred during the 7-day patch-free interval. It usually started 2 to 3 days after the third (last) cycle patch had been removed (Days 24 or 25) and could end either before or after the next patch had been applied. The subjects received diary cards to keep daily records on parameters of patch use (scheduled and unscheduled patch applications, reasons for unscheduled patches, patch-free intervals, application sites), vaginal bleeding intensity, pregnancy test results, and use of back-up contraception. A final examination was scheduled within 21 - 28 days after removal of the last study patch of Cycle 13 or in case of premature termination.
Indication/ Main Inclusion Criteria:	Indication: Prevention of pregnancy Main inclusion criteria: Healthy female subjects requesting contraception between 18 to 35 years of age (smokers 18 to 30 years) without contraindications for use of combined oral contraceptives; subjects with body mass index (BMI) >30.0 kg/m^2 were not included.
Study Objectives:	<u>Primary:</u> The primary objective of this study was to investigate the efficacy of the transdermal contraceptive patch (material no. 80876395, Transdermal Contraceptive Patch containing 0.55 mg EE and 2.1 mg GSD). <u>Secondary:</u> The secondary objectives were to investigate bleeding patterns, cycle control and the safety profile. Compliance and subjective assessment of satisfaction with the transdermal contraceptive patch were also evaluated.

Evaluation Criteria:	Efficacy (Primary): The primary variable was the occurrence of pregnancy (yes/no) while on treatment up to 7 days and up to 14 days (in the statistical analysis plan (SAP), analyses for up to 14 days after removal of the last patch were added) after removal of the last patch. Efficacy (Secondary): Bleeding pattern and cycle control. Safety: • Adverse events • Physical examination including vital signs and body weight • Pregnancy tests • Gynecological examination and breast palpation • Cytological cervix smear • Prior and concomitant medication
	Other: • Treatment compliance • Assessment of satisfaction with the transdermal contraceptive patch by the subjects
Statistical Methods:	Efficacy (Primary): For the number of pregnancies, the Pearl Index and a life table analysis along with the corresponding two-sided 95% confidence interval were provided. Efficacy (Secondary): Secondary efficacy variables were analyzed by descriptive statistics. Bleeding episode lengths were analyzed as descriptive statistics for the "mean", "maximum" and "range of length". The mean ± SD (standard deviation) values of each of these categories are presented, but it is not explicitly stated that these refer to the mean (± SD) of the "mean", mean of the "maximum" and mean of the "range". Safety: Safety variables were analyzed by descriptive statistics.
	Other: Other variables were analyzed by descriptive statistics.
Number of Subjects:	Planned: 1980 subjects to be screened, 1650 subjects to be treated. Analyzed: 1825 subjects were screened, 1694 subjects were admitted to treatment and 1631 subjects were treated (full analysis set, FAS).

Study Results
Results Summary — Subject Disposition and Baseline
Out of 1825 female subjects enrolled, 131 subjects failed the screening process; 4.2% of screened subjects were screening failures, 2.1% withdrew their consent, 0.9% were lost

to follow-up, and one subject (<0.1%) due to adverse event.

The remaining 1694 subjects completed screening and were admitted to study treatment. Among these 1694 subjects were 63 subjects (3.5% of the screened population) who were excluded from the full analysis set (subjects who had applied at least one patch and for whom at least one post-treatment observation was recorded were included in the full analysis set), specified as 26 subjects who "never took study drug" and 37 subjects with "no observation after treatment start".

The remaining 1631 subjects (100%) started treatment with Transdermal Contraceptive Patch and were included in the FAS (the FAS included 8 subjects who had received study treatment [dispensed at Visit 2] but were subsequently lost to follow-up; it was assumed (conservatively) that they had applied at least one patch).

The study was completed by 987 subjects (60.5% of the FAS). The study was prematurely discontinued by 644 subjects (39.5% of the FAS). The main reasons for discontinuation were adverse events (AEs) (14.3%) and withdrawal by subject (12.1%) and lost to follow-up (6.1%).

Completion of study treatment (the study treatment was completed if a subject applied at least one patch after Day 14 of Cycle 13 according to her diary, or whose completion date was available and this date was at least 350 days after start of study treatment) was recorded for 992 subjects (60.8%).

The mean (± SD) age of the full analysis set was 25.3 ± 4.4 years (range: 18.0 to 36.0 years; median 25.0 years). The mean BMI was 22.8 ± 3.0 kg/m^2 (range: 15.0 to 30.0 kg/m^2; median 22.4 kg/m^2). Most subjects in the study were White (1570 subjects; 96.3%); 0.6% were Black, 0.9% Asian, and 2.3% were other.

Results Summary — Efficacy

Over the course of this study which was planned for 13 cycles, the usage of 3 patches per cycle was most common and improved with time. The highest percentages of subjects had used 3 patches per cycle (approximately 45% of subjects in Cycle 1, increasing to 70% of subjects in Cycle 13); the next most frequent usages were 4 patches per cycle (approximately 30% of subjects in Cycle 1, decreasing to 20% of subjects in Cycle 13), and 5 patches per cycle (approximately 14% of subjects in Cycle 1, decreasing to 7% of subjects in Cycle 13).

The analyses of patch adhesion showed that higher numbers of patches had been applied to the abdomen (27282 patches) compared to the buttocks (19471 patches) or upper arm (10571 patches). There were also higher numbers of subjects who applied at least 1 patch to the abdomen compared to the buttocks or arm: 75.7% compared to 66.9% or 52.9% of subjects, respectively.

Complete patch detachments accounted for 5.7% of all applied patches; patch detachments that were either partial or complete were recorded for 15.3% of all patches. A higher percentage of patches were detached from the buttocks (7.2% completely; 18.3% partially/completely) compared to the abdomen (4.8% completely; 13.4% partially/completely) or the arm (5.0% completely; 14.7% partially/completely). By-cycle analyses showed decreasing numbers of complete detachments with time, from 321 subjects (20.1%) in Cycle 1 to 101 subjects (10.5%) in Cycle 13; the same was true for partial/complete detachments, with 834 subjects (52.2%) in Cycle 1 decreasing to 288 subjects (29.8%) in Cycle 13 who had at least one such detachment.

The primary efficacy variable for this study, the Pearl Index (PI), was based on a total of 14 pregnancies that occurred during treatment until 7 days after the removal of the last Transdermal Contraceptive Patch. The unadjusted PI (PI_U) was 1.19, and the upper limit of the 2-sided 95% confidence interval was 2.00. The difference between the PI_U (1.19) and the upper confidence limit (2.00) of the point estimate did not exceed 1.

No pregnancies occurred between 7 and 14 days after the removal of the last patch. Hence, the results for all PI calculations for pregnancies until 14 days after removal of the last patch were identical with the evaluations until 7 days after removal of the last patch.

Accounting for only 9 pregnancies regarded as "method failures", the adjusted PI (PI_A) was 0.81, and the upper limit of the 2-sided 95% confidence interval was 1.55. The difference between the PI_A (0.81) and the upper confidence limit (1.55) of the point estimate did not exceed 1.

The Kaplan-Meier estimator for Transdermal Contraceptive Patch after the last conception date (after 364 days of treatment) was 0.012 with a standard error of 0.00323. The probability of contraceptive protection after 364 days of treatment was 98.80%.

The evaluation of the secondary variable, the bleeding pattern based on reference periods of 90 days, showed a stable pattern. As expected, higher numbers of bleeding/spotting days were recorded in the first reference period (19.8 ± 8.1 days) because, per protocol, the first administration of the patch in period 1 started on the first day of bleeding. The mean number of bleeding/spotting days was 16.3 ± 5.9 days in reference period 2, 16.2 ± 5.5 days in reference period 3, and 15.7 ± 4.9 days in reference period 4, indicating a general trend to decrease over time.

A similar pattern for bleeding excluding spotting (i.e., bleeding-only) was observed, with higher numbers of bleeding-only days in period 1 (14.4 ± 5.4 days), and a trend to decrease over time in subsequent periods (12.1 ± 4.5 days in period 2, 12.0 ± 4.1 days in period 3, and 11.8 ± 4.1 days in period 4). Likewise, there were higher numbers of spotting-only days in period 1 (5.4 ± 5.9 days), and a trend to decrease over time in subsequent periods (4.1 ± 4.3 days in period 2, 4.1 ± 4.3 days in period 3, and 3.9 ± 3.8 days in period 4).

Considering period 2 onwards, no change was detected in the mean number of bleeding/spotting episodes over time, i.e., 3.3 ± 0.8 days in period 2, 3.3 ± 0.7 days in period 3, 3.3 ± 0.7 days in period 4. The average length of bleeding/spotting episodes (mean, maximum and range of length) decreased from reference period 2 (mean length 5.03 ± 1.55 days, maximum length 6.3 ± 3.1 days, range of length 2.4 ± 3.1 days) to reference period 4 (mean length 4.88 ± 1.31 days, maximum length 5.8 ± 2.2 days, range of length 1.7 ± 2.2 days).

Another secondary variable was the evaluation of cycle control parameters.

Accounting for treatment Cycle 1 until 12 only (although this study was planned for 13 treatment cycles, among the 1485 subjects who had diary entries for evaluation, only 283 subjects [approximately 19%] had returned completed diaries on Cycle 13. Almost all subjects (90.8% to 97.6%) in the FAS had reported withdrawal bleeding during the course of this study. Both the length (ranging from 4.9 ± 1.8 days to 5.1 ± 2.1 days) and onset (e.g., if hormone withdrawal is on Day 22 of the cycle and the withdrawal bleeding

episode starts on Day 25, then the onset is 3) (ranging from 2.7 ± 2.0 days to 3.0 ± 2.5 days) of withdrawal bleeding episodes were stable throughout the study. The maximum intensity score (intensity scores: 2 = spotting, 3 = light bleeding, 4 = normal bleeding, and 5 = heavy bleeding) of withdrawal bleeding was on average around 4 (i.e., normal bleeding).

Accounting for treatment Cycle 1 until 12 only, application deviation was recorded for 64 subjects and a corresponding bleeding event (application deviation bleeding) was rare, observed for 10 or fewer subjects in any cycle. There were fewer than 2 application bleeding/spotting days in any cycle, with mean values that ranged from 0.1 ± 0.2 days to 1.7 ± 7.7 days. An average of up to 0.2 (±0.4) days of application bleeding episodes was recorded in any treatment cycle, with a maximum of 2 episodes in any cycle. The average maximum length of application bleeding episodes ranged from 1.0 ± 0.0 days to 8.6 ± 16.4 days, with higher maxima in early compared to later cycles. The maximum intensity score of application deviation bleeding was on average around 3 (i.e., light bleeding), and ranged from 2.5 ± 0.8 to 3.7 ± 1.5.

Accounting for treatment Cycle 1 until 12 only, percentages of subjects with intracyclic bleeding/spotting were seen to decrease with time, from 169 subjects (11.4%) in Cycle 1, to 66 subjects (6.8%) in Cycle 12. Approximately half of these subjects reported intracyclic bleeding without spotting (i.e., bleeding-only) which likewise decreased with time, from 86 subjects (5.8%) in Cycle 1 to 27 subjects (2.8%) in Cycle 12. Around half an intracyclic bleeding/spotting day was reported in any cycle, with a mean of 0.1 ± 0.4 episodes of intracyclic bleeding/spotting in any cycle. The average maximum length of episodes of bleeding/spotting tended to decrease with time, from 6.1 ± 6.3 episodes in Cycle 1, to 4.7 ± 4.4 episodes in Cycle 12. The average maximum intensity score of intracyclic bleeding/spotting was relatively stable throughout the study, and ranged from 2.8 ± 1.0 to 3.1 ± 1.1.

At any time during Cycle 2 to 7 (collectively), intracyclic bleeding/spotting was reported by 491 subjects (34.6%) and intracyclic bleeding-only was reported by 288 subjects (20.3%). At any time during Cycles 2 to 13 (collectively), intracyclic bleeding/spotting was reported by 614 subjects (43.2%) and intracyclic bleeding-only was reported by 383 subjects (27.0%).

Results Summary — Safety

With 28 days per cycle, the planned total treatment duration was 364 days including the last patch-free interval. Subjects in the FAS had a mean treatment exposure of 272.9 days (SD 132.6 days, range: 1 to 468 days) excluding the last patch-free interval.

A total of 128 subjects (7.8%) in the FAS were reported with 160 pre-treatment adverse events. There were also 4 subjects in the listing-only set (LOS) with pre-treatment AEs during the screening phase regarded as serious: induced/spontaneous abortion for 3 subjects and premature baby for 1 subject.

A total of 1007 subjects (61.7%) were reported with 2822 treatment-emergent AEs (TEAEs), which were regarded as drug-related for 630 subjects (38.6%) with 1234 events.

The most frequently (>10% of the subjects) reported TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) were General disorders and administration site conditions in 433 subjects (26.5%), Infections and infestations in 428 subjects (26.2%), Reproductive system and breast disorders in 298 subjects (18.3%), and Nervous system disorders in 195 subjects (12.0%). The most frequently (>5% of subjects) reported TEAEs by MedDRA Preferred Term were headache in 155 subjects

(9.5%), followed by application site reaction in 139 subjects (8.5%), nasopharyngitis in 114 subjects (7.0%), and cervical dysplasia in 101 subjects (6.2%).

None of the subjects died during the study.

Treatment-emergent serious AEs (SAEs) were reported for 35 subjects (2.1%) with 42 events, and for another 4 subjects with 4 events whose (outcome) data were reported late and thus excluded from the database, tables (and percentages) presented in this report; the latter 4 events were abnormal pregnancy outcomes, mandated by the sponsor to be reported as SAEs. The SAEs were regarded as study drug-related for a total of 3 subjects (0.2%): depression and suicidal ideation (one subject), pulmonary embolism and deep vein thrombosis (another subject), pulmonary embolism and pulmonary infarction (a third subject).

A total of 5 subjects (0.3%) discontinued the study due to SAEs: these were the 2 subjects with drug-related pulmonary embolism (above), plus 3 more subjects with SAEs regarded as unrelated to the study drug. The latter 3 subjects (0.2%) had borderline personality disorder, epilepsy, and pancreatic pseudocyst.

A total of 234 subjects (14.3%) discontinued the study due to TEAEs, of those, 224 subjects (13.7%) discontinued due to drug-related TEAEs. The (drug-related) TEAEs most often causing discontinuation of the study drug were application site reactions in 52 subjects (3.2%), application site irritation in 24 subjects (1.5%) and application site hypersensitivity in 23 subjects (1.4%).

No clinically significant trends or safety signals were observed in the evaluation of other safety parameters. Vital signs were generally stable, and the majority of subjects had normal cervical smear results after completion of the study. Comparison of the frequency of prior medication (used by 73.5%) and concomitant medication (used by 47.0%) gave no indications that exposure to the study medication would lead to an increased overall need for medical treatment.

Results Summary — Other

Treatment compliance

The calculated overall mean compliance to patch use was acceptable, with a mean of 97.9% and a median of 100%.

Assessment of subjective satisfaction of the patch by the subjects

The assessment of subjective satisfaction was performed by 1502 (92.1%) subjects. Overall satisfaction was considered by more than one-third (40.4%) of the subjects as very satisfied, and by about one-third (33.6%) of the subjects as somewhat satisfied. A total of 12.8% of the subjects were neither satisfied nor dissatisfied and 10.5% were dissatisfied. Only few subjects (2.1%) were very dissatisfied.

Conclusion(s)

The results of this study confirmed the contraceptive efficacy of the Transdermal Contraceptive Patch. The bleeding pattern and cycle control were also acceptable. The safety profile of the Transdermal Contraceptive Patch did not reveal any unexpected findings related to the use of a hormonal contraceptive. The benefits of treatment with Transdermal Contraceptive Patch were demonstrated by the low Pearl Indices, the favorable menstrual bleeding patterns, and an adverse event profile consistent with the use of a transdermal hormonal contraceptive patch.

Publication(s):	None		
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