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:	14287	NCT00896571
Study Phase:	IIb	
Official Study Title:	Single-center, open-label, uncontrolled study to investigate the effects of the transdermal contraceptive patch containing 0.55 mg ethinylestradiol and 2.1 mg gestodene (material no. 80876395) on the endometrium in a 21-day regimen for 13 cycles in 80 healthy women	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Gestodene/EE Patch (BAY86-5016) Transdermal Patch	
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 peroral). Mode of administration: Transdermal Site: Outer upper arm, abdomen, or buttocks	
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:	02 JUL 2009
	Date of last subjects' last visit:	01 AUG 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	This study was conducted at a single center in Germany.	
Methodology:	This was a single-center, open-label, uncontrolled phase 2b study to investigate the effects of the Transdermal Contraceptive Patch on endometrium, contraceptive efficacy, and safety. Each subject received a diary card for recording the patch use. The subjects were seen by the investigator at Cycles 3, 7, 10, and 13 to ensure compliance and adequate reporting of adverse events (AEs). The visits took place between Days 7 and 21 of the respective	

	treatment cycle. A baseline endometrial biopsy was performed after screening (on Day 15 to 21 of the respective cycle). A second endometrial biopsy to assess the treatment effect was performed at Cycle 13 (on Day 7 to 21 of the cycle). A follow-up visit was planned 21 to 28 days after the removal of the last patch.
Indication/ Main Inclusion Criteria:	Indication: Prevention of pregnancy Main inclusion criteria: Female subjects requesting contraception between 18 and 35 years of age (smokers 18 to 30 years), with a normal endometrium, without contraindications for use of combined oral contraceptives, and in good general health; subjects with body mass index (BMI) >30.0 kg/m^2 were not included.
Study Objectives:	Primary: The primary objective of this study was to investigate the effect of the transdermal contraceptive patch containing 0.55 mg EE and 2.1 mg GSD on the endometrium. Secondary: The secondary objectives were contraceptive efficacy and safety profile.
Evaluation Criteria:	Pharmacodynamics: **Primary target variable:** The primary variable was the effect on the endometrium at Cycle 13. The protocol had defined the primary variable as "The effect on the endometrium at cycle 13". This non-specific definition based on the full analysis set (FAS) population would include "invalid" biopsies (e.g., from a subject who prematurely discontinued and was treated for less than 13 cycles who may have had endometrial biopsies taken between cycle Days 1 and 6 or after removal of the patch); based on the per-protocol set (PPS) population it would exclude "invalid" subjects (e.g., those with major protocol deviations, including subjects for whom it was uncertain whether a patch had been worn when the final biopsy was taken). To accurately evaluate the effect of the study treatment on the endometrium, a "restricted full analysis set" population was defined in the statistical analysis plan (SAP) and is regarded as the main analysis of the primary variable. The restricted FAS included subjects from the FAS who had received study treatment and had provided at least one post-baseline endometrial biopsy under treatment between cycle Days 7 and 21 (or thereafter for extended cycles). Efficacy (Primary): Number of pregnancies Efficacy (Secondary): Not applicable

	Safety: • Adverse events • Safety laboratory • Pregnancy tests • Physical examination including vital signs and body weight • 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:	Pharmacodynamics: Primary variable was analyzed by descriptive statistics. Efficacy (Primary): Descriptive statistics were used. Efficacy (Secondary): Not applicable Safety: Safety variables were analyzed by descriptive statistics.
	Other: Other variables were analyzed by descriptive statistics.
Number of Subjects:	Planned: 80 subjects entering treatment Analyzed: 92 subjects admitted to treatment 89 subjects treated (full analysis set) 53 subjects in the restricted FAS (primary variable only) 49 subjects in the per-protocol set

Study Results

Results Summary — Subject Disposition and Baseline

In total, 148 subjects signed informed consent and were enrolled in the study. Of those, 56 subjects were screening failures; most of them did not meet inclusion/exclusion criteria, others were lost to follow-up or withdrew their consent.

Of the 92 subjects admitted to treatment, 3 subjects never started treatment with Transdermal Contraceptive Patch. A total of 89 subjects (100%) started treatment with Transdermal Contraceptive Patch and had at least one observation after admission to treatment. They were included in the FAS.

The study treatment was completed by 57 subjects (64.0%). The study treatment was prematurely discontinued by 32 subjects because of AEs (18 subjects, 20.2%), withdrawal of consent (6 subjects, 6.7%), protocol deviation (2 subjects, 2.2%), lost to follow-up (2 subjects, 2.2%), other reasons (3 subjects, 3.4%), and pregnancy (1 subject, 1.1%).

The restricted FAS comprised 53 subjects.

Major protocol deviations preventing the inclusion of a subject in the per-protocol set were present in 40 subjects; for these subjects, the final endometrial biopsies had not been taken between Days 7 – 21 of the last treatment cycle (Cycle 13). The PPS comprised a total of 49 subjects without major protocol deviations.

In the FAS, the mean (± standard deviation [SD]) age of the subject sample was 25.4 ± 4.2 years (range: 18.0 to 34.0 years; median 25.0 years). With a BMI of on average 22.74 kg/m^2 (range: 15.6 to 29.9 kg/m^2) all women met the exclusion criterion (i.e., none was obese, BMI >30.0 kg/m^2).

The majority (84 subjects, 94.4%) of the subjects in the FAS were White, 2 subjects were Black/African American, 1 subject was Asian, and for 2 the race was recorded on the CRF as "multiple".

Results Summary — Pharmacodynamics

Endometrial biopsies were obtained to assess the primary variable: the effect of Transdermal Contraceptive Patch on the endometrium.

No one had an abnormal biopsy result.

All 89 subjects in the FAS had normal (categories of a [histologically] normal biopsy result were defined as atrophic, inactive, proliferative (weakly or active), secretory (cyclic or progestational) or menstrual) biopsy results at screening, a prerequisite for admission to treatment.

At the end of study treatment, all subjects with a post-baseline biopsy had normal biopsy results. Post-baseline biopsy results were available (for the FAS analysis, all available biopsy results irregardless of when the post-baseline biopsy was performed were included) for 59 subjects of the FAS which included all dropouts, 53 subjects of the restricted FAS who had >6 treatment cycles, and 49 subjects of the PPS who had 13 treatment cycles. In all analysis sets, adequate suppression of endometrial proliferation was shown in the majority of the subjects. As expected, most subjects in all analysis sets had an inactive or atrophic endometrium: 60.7% for the FAS, 66.1% for the restricted FAS, and 69.4% for the PPS. Specifically for the restricted FAS, the main analysis set of the primary variable, 49.1% of subjects had an inactive endometrium and 17.0% of subjects had an atrophic endometrium. This result confirms the effect of the hormonal patch on the endometrium.

Results Summary — Efficacy

Contraceptive efficacy in terms of numbers of pregnancies during treatment was acceptable, with a single pregnancy reported in the period of 13 treatment cycles until 7 days after removal of the last patch.

Results Summary — Safety

Safety was analyzed based on the FAS, which consisted of 89 subjects who had applied at least one patch and for whom at least one post-treatment observation was recorded. 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 266.7 days (SD 133.6 days, range 12.0 to 395.0 days) excluding the last patch-free interval.

Pre-treatment AEs were recorded for a total of 30 subjects (33.7%) in the FAS. There were 2 pre-treatment serious adverse events (SAEs) of listing only set (LOS) subjects who never had started with the patch application (fatigue and arrested labor for one subject; appendicitis for another subject).

After patch application, 80 (89.9%) of the 89 subjects in the FAS reported treatment-emergent AEs (TEAEs). Of those, 65 subjects (73.0%) reported study drug-related TEAEs.

The most frequently (>25% of the subjects) reported TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) were General disorders and administration site conditions (57.3%), Reproductive system and breast disorders (47.2%), and Infections and infestations (29.2%).

The most frequently (>20% of subjects) occurring TEAEs by MedDRA preferred terms were application site reaction (27.0%), application site erythema (23.6%), and metrorrhagia (21.3%). These were also the most frequently occurring study drug-related TEAEs (with 27.0%, 23.6%, and 20.2% for application site reaction, application site erythema, and metrorrhagia, respectively). Other more frequently reported TEAEs regarded as study drug-related were application site pruritus (13.5%), mood swings (9.0%), and dysmenorrhea (6.7%), whereas all other events were reported by fewer than 5% of the subjects. These events were expected of the young female population using a transdermal contraceptive product.

No subject died. In total, 7 treatment-emergent SAEs were reported for 4 subjects: one subject who prematurely discontinued the study with lower abdominal pain and salpingo-oophoritis, another subject with appendicitis, one more subject with induced abortion (2 events; this subject had an induced abortion followed by a re-curettage due to pain consistent with residua post abruptionem), and in addition one more subject with pyelonephritis (2 events). No SAE was related to the study medication and all subjects recovered from the events.

A total of 18 subjects (20.2%) prematurely discontinued the study due to TEAEs (including the unrelated SAEs of subject who prematurely discontinued the study with lower abdominal pain and salpingo-oophoritis as mentioned above). Of those, 17 subjects (19.1%) discontinued due to study drug-related events, largely due to drug-related TEAEs that were skin reactions from the SOC General disorders and administration site conditions (in 11.2% of the subjects) or TEAEs from the SOC Reproductive system and breast disorders (in 6.7% of the subjects).

By application site, a higher percentage of skin reactions was recorded for patches applied to the arms (31.5% of subjects), compared to the abdomen (18.0% of subjects) or the buttocks (10.1% of subjects). Absolute numbers of patches applied were also highest on the arms (1157 patches) compared to abdomen (1083 patches), and buttocks (913 patches). Similarly, over the entire treatment period, more subjects had applied at least 1 patch to the arms than to the abdomen or the buttocks (75.3%, 66.3%, and 58.4% of the subjects, respectively).

All endometrial biopsies were normal (results are summarized above).

No clinically significant trends or safety signals were observed in the evaluation of other safety parameters.

Most laboratory values were within normal limits at baseline and during the study. Vital signs and body weight were 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 all subjects, 100%) and concomitant medication (used by 78.7%) 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 mean compliance to patch use was excellent, both in the FAS (mean 97.9%, median 100%) and the PPS (mean 99.7%, median 100%).

Over the entire treatment period of 13 cycles, complete patch detachments accounted for about 8% of all patches (7.3% in the FAS, 7.8% in the PPS); patch detachments that were either partial or complete were recorded for approximately 17% of all applied patches.

Analyses of numbers of patches showed a trend to higher average numbers of patches applied to the arm by subjects in both the FAS (arms 13.0 ± 15.7 patches; abdomen 12.2 ± 14.8 patches; buttocks 10.3 ± 14.1 patches) and the PPS (arms 17.3 ± 17.0 patches; abdomen 15.1 ± 16.7 patches; buttocks 15.2 ± 16.7 patches). This result was consistent with the overall analyses of numbers of subjects who applied at least 1 patch to either the arms, abdomen, or buttocks: 75.3%, 66.3%, and 58.4% of the subjects in the FAS and 83.7%, 67.3%, and 69.4% of the subjects in the PPS. By-cycle analyses showed a similar average number of patches applied to arms or abdomen during the later treatment cycles.

Assessment of satisfaction with the transdermal contraceptive patch by the subjects:

Overall satisfaction with the patch was good. More than half of the subjects (55.2%) were either very satisfied or somewhat satisfied with the patch (very satisfied 20.7%; somewhat satisfied 34.5%). Only a few subjects were very dissatisfied (6.9%), and about a third of the subjects were either ambivalent (6.9%) or dissatisfied (24.1%) with the patch.

Conclusion(s)

The results of this study showed the expected endometrial effect of the transdermal contraceptive patch when used over 13 treatment cycles. At the end of treatment, the majority of subjects had an inactive or atrophic endometrium.

Contraceptive reliability of Transdermal Contraceptive Patch was acceptable.

The general safety profile of Transdermal Contraceptive Patch gave no reason for concern.

Publication(s):	None		
Date Created or Date Last Updated:	14 MAY 2012	Date of Clinical Study Report:	30 JAN 2012