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:	91557	NCT00933179
Study Phase:	IIb	
Official Study Title:	A single-center, open-label, crossover, randomized study to investigate the impact of the transdermal contraceptive patch containing 0.55 mg ethinylestradiol and 2.1 mg gestodene (material no. 80876395) in a 21-day regimen as compared to a monophasic contraceptive containing ethinylestradiol and levonorgestrel (0.03 mg/0.15 mg) in a 21-day regimen on hemostatic parameters in 30 women aged 18 – 35 years over 3 treatment cycles in each period	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EE/GSD (BAY 86-5016) Transdermal contraceptive patch (Material no. 80876395), FC-Patch Low	
Name of Active Ingredient:	Ethinylestradiol (EE) and gestodene (GSD)	
Dose and Mode of Administration:	Dose: 0.55 mg EE per patch, daily delivery rate approximately 8 µg; equivalent to approximately 18 µg per oral (po). 2.1 mg GSD per patch, daily delivery rate approximately 55 µg; equivalent to approximately 55 µg po. Mode of administration: Transdermal	
Reference Therapy/Placebo		
Reference Therapy:	Microgynon	
Dose and Mode of Administration:	Dose: 0.03 mg EE per tablet and 0.15 mg levonorgestrel (LNG) per tablet Mode of administration: Oral	
Duration of Treatment:	Test therapy: 21-day regimen per cycle (1 patch a week for 3 weeks followed by a 7-day patch-free interval) for 3 cycles Reference therapy: 21-day regimen per cycle (1 tablet a day for 3 weeks followed by a 7-day tablet-free interval) for 3 cycles	
Studied period:	Date of first subjects' first visit:	30 JUN 2009
	Date of last subjects' last visit:	27 SEP 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	The study was conducted at a single center in Germany.	

Methodology:	All subjects seeking contraception were recruited and randomized 1:1 into one of the following 2 treatment sequences: Sequence A: 3 treatment cycles with the FC-Patch low (investigational product) in Period 1, followed by 2 washout cycles, followed by 3 treatment cycles with Microgynon (reference product) in Period 2. Sequence B: 3 treatment cycles with Microgynon (reference product) in Period 1, followed by 2 washout cycles, followed by 3 treatment cycles with FC-Patch low (investigational product) in Period 2. Visit 1 was the screening visit and was performed within a maximum of 12 weeks prior to the start of the treatment cycle. Before start of treatment, 2 washout cycles (1 and 2) were required. Visit 2 took place during Washout Cycle 2 (Days 15 – 21). Visits 3 took place during Treatment Cycle 3 (Days 15 – 21) in treatment Period 1. Visit 4 took place during the subsequent Washout cycle 3 and Visit 5 took place during Washout Cycle 4 (Days 15 – 21). Visit 6 took place during Treatment Cycle 6 (Days 15 – 21) in treatment Period 2. A follow-up visit (Visit 7) was held within 21 – 28 days after removal of the final patch/intake of the last tablet. This visit was also performed in the event of premature discontinuation of treatment.
Indication/ Main Inclusion Criteria:	Indication Prevention of pregnancy Main inclusion criteria: Women between 18 and 35 years (inclusive) of age who requested contraception, smokers with a maximum age of 30 years at the time of informed consent.
Study Objectives:	<u>Primary:</u> The primary objective was to investigate the impact of the transdermal contraceptive patch containing 0.55 mg EE and 2.1 mg GSD in a 21-day regimen (FC-Patch low) on hemostasis parameters, in comparison to a combined oral contraceptive containing 0.03 mg EE and 0.15 mg LNG in a 21-day regimen (Microgynon). <u>Secondary:</u> The secondary objectives were the contraceptive efficacy, bleeding pattern, cycle control, and the safety profile (including carbohydrate and lipid metabolism) of FC-Patch low in comparison to Microgynon.
Evaluation Criteria:	<u>Efficacy (Primary):</u> The following efficacy variables were analyzed: • Bleeding pattern • Cycle control • Number of unintended pregnancies

	Efficacy (Secondary): Not applicable Safety: The primary variables of the study were the intra-individual absolute changes from baseline to treatment of the following 2 hemostasis parameters: prothrombin fragments 1 + 2 and D-dimer. Secondary variables of the study were the absolute and relative changes from corresponding baseline values for the following hemostasis parameters: • Procoagulatory parameters: ➢ Fibrinogen ➢ Factor VII activity (VIIc) ➢ Factor VIII activity (VIIIc) • Anticoagulatory parameters: ➢ Antithrombin III (activity) ➢ Protein C (activity) ➢ Protein S (activity) ➢ Activated Protein C (APC) resistance (based on the activated partial thromboplastin time) ➢ APC sensitivity (according to Rosing) • Thrombin and fibrin turnover (activating marker) parameter: ➢ Prothrombin (Factor II) Other safety variables were: • Safety laboratory (including lipid and carbohydrate metabolism) • Sex hormone binding globulin (SHBG) • Adverse events (AEs) • Pregnancy tests • Physical examination, vital signs, 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 subject
Statistical Methods:	Efficacy (Primary): Descriptive statistics was used for calculation of bleeding pattern and cycle control. Efficacy (Secondary):

	Not applicable Safety: Primary variables: Statistical two-sided test for non-zero treatment effect in at least one of the primary variables (adjusting for multiplicity by using Bonferroni correction to achieve a significance level of 5%), derived from ANOVA models that include a random subject intercept, and 97.5% confidence intervals for the treatment effect for each of the primary variables. Secondary variables were analyzed as described for the primary variables. Descriptive statistics were used for all other safety variables. All AEs were coded according to MedDRA version 14, and classified as pretreatment or treatment-emergent (TEAEs).
	Other Treatment compliance and subjective assessment of satisfaction were summarized using descriptive statistics.
Number of Subjects:	Planned: 30 subjects in total 15 subjects randomized to treatment sequence A 15 subject randomized to treatment sequence B Analyzed: 30 randomized, 29 received treatment Full analysis set (FAS) 15 subjects in treatment sequence A 14 subjects in treatment sequence B

Study Results

Results Summary — Subject Disposition and Baseline

A total of 48 female subjects signed informed consent, were enrolled into the study, and screened in 1 study center in Germany. Among them, 18 subjects failed the screening process and were not included in the study. Of the remaining 30 subjects who were randomized to receive treatment, 1 subject randomized to Sequence B withdrew consent from the study and never received treatment. In all, 29 subjects actually received study treatment. These 29 subjects performed the first washout phase and started treatment Period 1: Fifteen (15) subjects (100.0%) in Sequence A, and 14 subjects (100.0%) in Sequence B. This population constituted the FAS and provided data for analysis after the start of study treatment. All 29 subjects completed treatment Period 1 and performed the second washout phase.

During the second washout phase, 1 subject became pregnant and discontinued the study. The remaining 28 subjects started treatment Period 2, which was completed by a total of 26 subjects: 13 subjects (86.7%) in Sequence A, and 13 subjects (92.9%) in Sequence B.

A total of 3 subjects (10.3%) who received any study treatment prematurely discontinued the study for the following reasons: lost to follow-up during treatment Period 2: 1 subject (6.7%) in Sequence A, protocol deviation during treatment Period 2: 1 subject (6.7%) in Sequence A, pregnancy during the second washout phase: 1 subject (6.7%) in Sequence B.

The remaining population without major protocol deviations made up the per-protocol set (PPS), comprising a total of 26 subjects, among them 13 subjects in Sequence A, and 13 subjects in Sequence B.

The mean (± standard deviation [SD]) age of the study population as a whole was 27.0 ± 4.6 years (range: 18.0 to 35.0 years; median 28.0 years) and was similar for subjects in both treatment sequences. The mean values for height (overall 167.1 ± 5.8 cm), body weight (overall 62.6 ± 7.9 kg), and body mass index (BMI; overall 22.4 ± 2.6 kg/m^2) were also similar between the treatment sequences. Except for 2 Asian subjects (6.9%), one in each treatment sequence, all other subjects in the FAS were White (93.1%).

There was no medically relevant difference between treatment sequences observed for medical history findings in any SOC. On average, subjects in both treatment sequences reported fewer than one birth (0.4 ± 0.8) or one abortion (0.1 ± 0.4). The time to last birth or abortion was longer on average for subjects in Sequence A (2244 ± 2167 days) than those in Sequence B (1440 ± 918 days). Two subjects in Sequence A only reported having experienced intracyclic vaginal bleeding within the last 6 months. There was no difference in the use of different types of contraceptive methods between the 2 groups.

Results Summary — Safety

Primary efficacy variables

Prothrombin fragments 1+2

Absolute changes and ANOVA of FAS

There were no statistically significant differences between the treatment groups in both treatment periods. Whereas in the first treatment period for both treatments hardly any change for Prothrombin fragments 1+2 could be observed (absolute change -0.007 nmol/L and -0.001 nmol/L in the first treatment period while under FC-Patch and Microgynon, respectively), an increase in the second treatment period was observed (absolute change 0.025 nmol/L and 0.028 nmol/L in the second treatment period while under FC-Patch and Microgynon, respectively).

Accounting for both treatment periods, the overall mean absolute change was 0.008 nmol/L for FC-Patch low and 0.013 nmol/L for Microgynon. The treatment difference of -0.00 with a 2-sided confidence interval of [-0.032; 0.022] was not statistically significant (p = 0.667), i.e., there was no difference between FC-Patch low and Microgynon. There were no statistically significant sequences or period effects.

In both treatment groups, the majority of subjects (75%) either had values within the respective reference ranges at any time-point or had out-of range values during the study which returned to within-range at the final visit.

Two subjects (7.1%) had high Prothrombin fragments 1+2 values under FC-Patch low and one subject (3.6%) under Microgynon. Two subjects (8.0%) were reported with treatment-emergent levels below reference range under FC-Patch low, 6 (21.4%) under Microgynon. None of the values under treatment were assessed as clinically significant.

The results for the PPS population were very similar to the FAS and are not described.

D-dimer

Absolute changes and ANOVA of FAS

There were no statistically significant differences between the treatment groups in both treatment periods. The increase in the first treatment period was slightly smaller than in the second treatment period (absolute change 95.33 nmol/L and 103.79 nmol/L in the first treatment period compared with 120.46 nmol/L and 124.39 nmol/L in the second treatment period while under FC-Patch and Microgynon, respectively).

Accounting for both treatment periods, the overall mean absolute change was 107.00 nmol/L for FC-Patch low and 113.70 nmol/L for Microgynon. The treatment difference of -6.19 with a 2-sided confidence interval of [-103; 90.916] was not statistically significant (p = 0.884), i.e., there was no difference between FC-Patch low and Microgynon.

In both treatment groups, the majority of subjects (>92%) either had values within the respective reference range at any time-point or had out-of range values during the study which returned to within-range at the final visit. Two subjects (7.1%) on FC-Patch low and 3 subjects (10.7%) on Microgynon had treatment-emergent high levels of D-dimer. None of these deviations from the reference range were regarded as clinically significant.

The results for the PPS population were very similar to the FAS and are not described.

In summary, the primary hemostasis variables changed comparably for both therapies during treatment. The observed increase for D-dimer in both treatment periods and for Prothrombin in the second period implies that the overall balance between the different factors influencing hemostasis was maintained on an unregulated level.

Table 1 displays the results of the primary target variables for the FAS.

Table 1: Primary hemostasis parameters: mean absolute and relative changes, and analysis of treatment differences (FAS)

Primary hemostasis parameters	Mean values (from baseline to final value) per treatment period			
	FC-Patch low		Microgynon	
	Period 1	Period 2	Period 1	Period 2
Absolute changes				
Prothrombin fragments 1+2	- 0.007	+ 0.025	- 0.001	+ 0.028
D-dimer	+ 95.33	+ 120.46	+ 103.79	+ 124.39
Relative changes				
Prothrombin fragments 1+2	- 4.809	+ 29.951	- 0.507	+ 26.776
D-dimer	+ 58.61	+ 90.12	+ 71.25	+ 79.96

Analyses by ANOVA	Mean absolute change [a]		Mean treatment difference	Confidence interval	p-value
	FC-Patch low	Microgynon			
Prothrombin fragments 1+2	+ 0.008	+ 0.013	- 0.00	[-0.032; 0.022]	0.667
D-dimer	+ 107.00	+ 113.70	- 6.19	[-103 ; 90.916]	0.884

[a] Accounting for both treatment periods

Note: Subjects treated in Period 1 are different from those treated in Period 2

Secondary efficacy variables

Absolute changes– Prothrombin (Factor II)

For FC-Patch low the increases were the same in the two treatment periods (17.3% in first treatment period, 16.9% in the second). They were smaller under Microgynon treatment (1.5% absolute change in first treatment period, 9.0% in the second).

Absolute changes – (pro)coagulatory parameters

The (pro)coagulatory parameters evaluated were Fibrinogen, Factor VII activity, and Factor VIII activity.

There were only minimal changes in Factor VIII activity under FC-Patch low or Microgynon treatment and small increases in fibrinogen under the two treatments in both periods. There was no change in Factor VII activity under Microgynon treatment, but an increase in the two treatment periods under treatment with FC-Patch low. Absolute changes while under FC Patch low were 21.47% in the first treatment period and 25.46% in Factor VII activity (VIIc) with 23% subjects turning to elevated levels after normal levels at baseline in first treatment period and 63% subjects in the second treatment period. Baseline values were between 90.50% and 109.07%.

Absolute changes – anticoagulatory parameters

The anticoagulatory parameters evaluated were Antithrombin III, Protein C, Protein S, APC resistance, and APC sensitivity.

Antithrombin III and Protein C levels did not change remarkably from baseline under FC-Patch low or Microgynon in any of the treatment periods. Protein S and APC resistance level decreases from baseline were small and no subject had levels outside the reference ranges. APC sensitivity level changes from baseline were obvious with increases to levels about twice as high as baseline. Increases of 1.71 and 2.58 were observed while under FC-Patch low in the first and second treatment period, respectively, and increases of 2.08 in the first and 1.42 in the second treatment period while under Microgynon treatment. Baseline values were between 1.83 and 2.38. Reference ranges (i.e., value above 2.2) were exceeded by up to 100% of the subjects in treatment cycle 3 of the two treatments. Median values at baseline were close to the upper limit of the reference ranges (i.e., 2.05) for the first treatment period while under Microgynon (2.00; 1.60 for FC-Patch low) and all mean values for respective treatment cycle 3 were above the reference ranges for both treatments. None of the deviations from reference range were regarded as clinically significant.

Other safety variables:

Adverse events

No deaths were reported in this study. There were no serious AEs reported in this study.

A total of 100 TEAEs were reported in the FAS: 65 events in 21 subjects (72.4%) while on FC-Patch low and 35 events in 18 subjects (62.1%) while on Microgynon. None of the

subjects prematurely discontinued the study due to TEAEs.

Most frequent AEs were nasopharyngitis with 18 events in 13 (44.8%) subjects while under FC-Patch low, and 15 events in 12 (41.4%) subjects while under Microgynon, followed by headache; 8 events in 4 (13.8%) subjects while under FC-Patch low, and 6 events in 3 (10.3%) subjects while under Microgynon.

A total of 12 TEAEs were regarded as study drug-related: 10 events in 5 subjects (17.2%) while on FC-Patch low (mild in 4, moderate in 1 subject), and 2 events in 2 subjects (6.9%, all mild AEs) while on Microgynon. Events occurring more than once were application site erythema and increased weight with 2 events in 2 subjects each, both occurring only in the FC-Patch low period. Headache, application site reaction, application site pruritus, and application site irritation occurred each in one subject in the FC-Patch low treatment period. The 2 events reported of subjects while under Microgynon, that were assessed to be study drug-related, were decreased weight and acne.

TEAEs were either mild or moderate in intensity. Most frequent Preferred terms (PTs) that were assessed as moderate were headache and migraine without aura. Severe TEAEs did not occur in this study. All but one subject recovered/resolved from their TEAEs (21 subjects while under FC-Patch low; 18 while under Microgynon); one subject of the FC-Patch low group (3.4%) had additionally an unknown outcome of her cervicitis.

One pregnancy occurred during the 2nd washout phase of this study after intake of the last tablet of Microgynon.

Laboratory parameters

Under both treatments, the vast majority of subjects either had laboratory values for most parameters within the respective reference ranges at any time-point or had out-of range values during the study which returned to within-range at the final visit. Single events of clinically significant abnormal laboratory values in the relevant alert ranges occurred, but mostly returned to normal range values by the end of the study. Of those 4 subjects with clinically significantly deviating values during the study and still abnormal values in the last examination, three had laboratory values below (platelet count in PID 100010001 and protein level in PID 100010022) or above (SHBG level in PID 10010034) the reference ranges already at screening. PID 10010024 had a normal hemoglobin level at screening and low values throughout the study. The value at Visit 6 was assessed to be clinically significantly low with 9.4 g/dL. By the end of the study it was 10.5 g/dL, therefore still low, but not assessed as clinically significant.

Almost all subjects had hematology values (i.e., erythrocytes, leukocytes and platelets) within the reference ranges. Some subjects (up to over 35% under treatment with Microgynon and over 30% under treatment with FC-Patch low) had hemoglobin values below the lower range of the reference ranges, highest proportions were observed in the wash-out or follow-up period. Most subjects had values within the reference ranges for the liver enzymes and for cholinesterase, total bilirubin. Increases of subjects with low values below the lower limit of the reference ranges for triglycerides were observed under both treatments and both sequences with up to 40% of subjects. Trends to low values for HDL- (only under FC-Patch low treatment) and LDL cholesterol (more frequent under Microgynon) were observed in up to 21% of subjects. Increases of proportions of subjects with values below the reference ranges were observed for total protein, in up to 30% in the follow-up phase after FC-Patch low treatment as second treatment.

SHBG was found to be above the upper limit of the reference ranges in 23 of 24 subjects under FC-Patch low and in 8 of 24 subjects while under Microgynon.

Other safety parameters

The heart rate, blood pressure, body weight and consequently also the BMI values before treatment were similar in both treatment sequences and did not change under treatment.

For one subject who first started with Microgynon and then was treated with FC-Patch low, an abnormal cervical smear result was reported at Day 243 of the study course. At this time, the subject had a cervicitis reported as AE. The AE outcome was still unknown by the end of the study. All other subjects had normal cervical smears before and after treatment.

Results Summary — Efficacy

Bleeding pattern

The results are described below in detail for the FAS for the reference period of 90 days. A similar pattern of results was observed for the PPS. Subjects in both treatment groups had similar mean numbers of bleeding/spotting days (FC-Patch low 27.5 ± 9.5 days, Microgynon 25.9 ± 8.7 days. No differences were seen regarding mean numbers of bleeding/spotting episodes (FC-Patch low 3.6 ± 1.1, Microgynon 3.3 ± 0.7), mean length of episodes (FC-Patch low 5.4 ± 1.4 days, Microgynon 5.5 ± 1.9 days), maximum length of episodes (FC-Patch low 7.2 ± 2.7 days, Microgynon 7.0 ± 3.1 days), or range of length of episodes (FC-Patch low 3.5 ± 3.2 days, Microgynon 3.2 ± 3.2 days).

Cycle control

The results are described below for the FAS. A similar pattern of results was obtained for the PPS. Nearly all subjects with data reported experiencing withdrawal bleeding in all treatment cycles. Up to a third of subjects with data reported having intracyclic bleeding/spotting (maximum 30.8% in second treatment period under FC-Patch low, 25.0% in second treatment period under Microgynon). No one had application deviation bleeding.

Number of unintended pregnancies

No pregnancy occurred under treatment in this study. One pregnancy occurred but during the second washout phase of the study (during the 2 washout cycles between the 2 treatment periods, subjects were required to use non-hormonal contraception (e.g., condoms, spermicide or diaphragm).

Results Summary — Other

Treatment compliance

The overall compliance to treatment with FC-Patch low was excellent (i.e., mean values of nearly 100%), estimated at 99.89% (SD 0.38, range 98.5 to 100.0) for the FAS, and 99.88% (SD 0.39, range 98.5 to 100.0) for the PPS. The overall compliance to treatment with Microgynon was excellent (i.e., mean values of nearly 100%), estimated at 98.59% (SD 2.50, range 90.48 to 100.0) for the FAS, and 98.90% (SD 1.95, range 93.65 to 100.0) for the PPS

Assessment of satisfaction with the transdermal contraceptive patch by the subject

The majority of subjects assessed the patch as convenient and were satisfied with the patch. The characteristics of the patch that were liked by most subjects were the low hormone dose of the patch, to have to think about contraception once a week, the reliability of the patch, and that one does not have to swallow anything. Most disliked characteristics of the patch were the dirty edges and that the patch edges detached. Over 58% of the subjects rated the patch much better or chose the second best rating compared to the previous method of contraception.

Conclusion(s)

The balance of the coagulatory system appeared to be maintained at an up-regulated level for both the pro-and the anticoagulatory parameters in both treatment sequences. There was no statistical difference between the treatments for the primary hemostasis parameters D-dimer and Prothrombin Fragments 1+2 tested for significance and none of these values for under treatment were assessed as clinically significant.

It can be concluded that both treatments used in the study were safe and well tolerated by the subjects, and the overall safety profile gave no reasons for any safety concerns. No unfavourable changes of any clinical significance were observed.

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