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:	13082	NCT00984789 EudraCT Number: 2008-007308-27
Study Phase:	IIIa	
Official Study Title:	Multi-center, open-label, randomized, parallel-group comparison of cycle control, bleeding pattern, lipid and carbohydrate metabolism of the transdermal contraceptive patch containing 0.55 mg ethinylestradiol and 2.1 mg gestodene (material no. 80876395) in a 21-day regimen vs. a comparator patch EVRA (0.6 mg ethinylestradiol and 6 mg norelgestromin) in a 21 day regimen for 7 cycles in 400 women	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	FC-Patch Low	
Name of Active Ingredient:	Ethinylestradiol (EE) and gestodene (GSD)	
Dose and Mode of Administration:	Each 11 cm^2 transdermal patch contains 0.55 mg ethinylestradiol and 2.10 mg gestodene. Each transdermal patch releases 0.013 mg ethinylestradiol (equal to oral doses of 0.02 mg) and 0.06 mg gestodene per 24 hours. Transdermal	
Reference Therapy/Placebo		
Reference Therapy:	EVRA	
Dose and Mode of Administration:	Each patch contains 0.6 mg EE and 6 mg norelgestromin (NGMN) Transdermal	
Duration of Treatment:	21 day regimen per cycle (1 patch per week for 3 weeks, followed by 7-day patch-free interval) for 7 cycles	
Studied period:	**Date of first subjects' first visit:**	9 May 2009
	Date of last subjects' last visit:	3 Sep 2010
Study Center(s):	24 investigational sites treated subjects in 3 countries: 11 centers in Austria, 9 centers in the Czech Republic, 4 centers in The Netherlands	
Methodology:	Record uterine bleeding and patch use on diary cards, document adverse events (AEs), blood sample analyses for pharmacokinetics (EE, GSD and SHBG) and safety laboratory analyses (hematology, lipid and chemistry), physical and gynecological examinations, subject questionnaire.	

Indication/ Main Inclusion Criteria:	Prevention of pregnancy Women from 18 to 35 years of age (inclusive), who requested contraception; smokers with a maximum age of 30 years at time of informed consent, subjects with body mass index (BMI) > 30.0 kg/m2 not included
Study Objectives:	**Primary:** To investigate the bleeding pattern and cycle control parameters of the transdermal contraceptive patch FC-Patch low (0.55 mg EE and 2.1 mg GSD) in comparison to EVRA (0.6 mg EE and 6 mg NGMN. **Secondary:** To investigate the contraceptive efficacy, the safety profile (including lipid/carbohydrate metabolism), pharmacokinetics (PK), compliance and subjective assessment treatment with FC-Patch Low compared to EVRA.
Evaluation Criteria:	**Efficacy (Primary):** Analysis of the bleeding pattern and cycle control parameters. **Efficacy (Secondary):** Contraceptive efficacy, i.e. the number of pregnancies while on treatment up to 7 days after removal of the last patch. **Safety:** Analysis of adverse events (AEs), assessment of hematology, lipid and chemistry laboratory parameters, evaluation of cervical smears, vital signs, body weight and height (at baseline).
	Pharmacokinetics: Analyses (AUC, Cmax) of EE for FC-Patch Low or EVRA, and of GSD and SHBG for FC-Patch Low. **Other:** Compliance and subjective assessment of treatment.
Statistical Methods:	**Efficacy (Primary) - if applicable:** Descriptive statistics. **Efficacy (Secondary) - if applicable:** Descriptive statistics. **Safety:** Descriptive statistics.

	Pharmacokinetics: Descriptive statistics. **Other:** Descriptive statistics.
Number of Subjects:	398 subjects were treated (full analysis set, FAS), i.e. 200 subjects on FC-Patch Low and 198 subjects on EVRA

Study Results

Results Summary — Subject Disposition and Baseline

Of the 432 female subjects who were enrolled in the study, 26 failed screening and 406 were randomized for treatment with either FC-Patch Low (204) or EVRA (202). 8 randomized subjects (4 from each group) never administered the study medication.

398 subjects (100%, FAS) were treated with either FC-Patch Low (200) or EVRA (198). 342 subjects (85.9%) in the FAS completed study medication: 169 subjects (84.5%) on FC-Patch Low and 173 subjects (87.4%) on EVRA. 337 subjects (83.0%) completed the study: 167 subjects (81.9%) on FC-Patch Low and 170 subjects (84.2%) on EVRA.

69 subjects (17.0%) prematurely discontinued the study, primarily due to AEs (FC-Patch Low 8.8%, EVRA 3.5%) or withdrawal by the subject (FC-Patch Low 5.4%, EVRA 5.9%).

Baseline features of the 2 treatment groups in the FAS were well matched. Mean (± SD) age was 24.7±4.4 years, BMI was 22.1±2.8 kg/m2, 26.6% of subjects were current smokers, most were either light users (66.8%) or non-users (31.9%) of alcohol, >90% of subjects had at least secondary education, and all were White. Usage of concomitant medication was similar between the treatment groups.

Results Summary — Efficacy

The bleeding pattern (primary variable) was evaluated using reference periods of 90 days. There was a decrease in numbers of bleeding/spotting days from period 1 to 2 for FC-Patch Low (mean±SD from 19.7±6.6 days to 15.7±4.0 days, respectively) and for EVRA (20.6±6.5 days to 18.4±6.2 days), with corresponding decreases in bleeding-only and spotting-only days. Period 2 showed 2.3 bleeding-only days less, 0.5 spotting-only days less, and 2.7 bleeding/spotting days less for FC-Patch Low compared to EVRA. The number of bleeding/spotting episodes was stable from period 1 to 2 in both groups (3.3±0.8 days). The length of bleeding/spotting episodes (mean, maximum and range of length) decreased from period 1 to 2, and was lower for FC-Patch Low (period 2: mean length 5.07±1.33 days, maximum length 6.0±2.3 days, range of length 1.9±2.3 days) than for EVRA (period 2: mean length 5.66±1.44 days, maximum length 6.8±2.4 days, range of length 2.3±2.7 days).

Cycle control evaluations showed that the length of withdrawal bleeding episodes was stable, and lower in the FC-Patch Low group compared to EVRA (e.g. 5.0±1.2 days vs. 5.7±1.8 days in Cycle 5). Withdrawal bleeding onset was marginally shorter for FC-Patch Low (2.4±1.3 days to 2.8±2.1 days) than for EVRA (2.7±2.5 days to 3.1±2.6 days). Normal bleeding intensities were mainly recorded, with lower average intensity scores for FC-Patch Low (3.8±0.7 to 4.1±0.7) than for EVRA (4.0±0.7 to 4.2±0.6). Lower percentages of subjects had normal or heavy bleeding with FC-Patch Low (normal 54.8%-61.4%, heavy 12.9%-27.7%) than with EVRA (normal 59.1%-68.4%; heavy 22.0%-28.5%).

2 subjects on EVRA had single application deviation bleeding episodes. In both groups, intracyclic bleeding/spotting occurred in 6%-11% of subjects per cycle, a third (2.2%-4.3%) of which were bleeding-only instances. Subjects in both groups had up to 2 intracyclic bleeding/spotting or bleeding-only episodes in any cycle, similar lengths of bleeding/spotting episodes (3-7 days) and intracyclic bleeding which was mostly of spotting to light intensity. The average length of bleeding-only episodes was more variable for the FC-Patch Low group (5.0±6.0 days to 14.5±14.0 days) than for EVRA (4.3±0.6 days to 9.3±8.1 days).

The number of subjects with intracyclic bleeding/spotting episodes at any time between Cycles 2 until 7 (secondary variable) was similar between the treatment groups (FC-Patch Low vs. EVRA) with the FAS (29.8% vs. 28.2% of subjects, respectively) but was 6.3% higher for FC-Patch Low with the PPS (33.9% vs. 27.6%, respectively). Numbers of subjects with intracyclic bleeding-only episodes were 16.0% vs. 11.7%, respectively in the FAS (difference of 4.3%) and 16.1% vs. 11.0%, respectively in the PPS (difference of 5.1%).

There was 1 pregnancy during treatment in the FC-Patch Low group and none in the EVRA group, 2 pre-treatment pregnancies and 2 post-treatment pregnancies.

Results Summary — Safety

Safety analysis was done on data from the FAS. Total exposure (mean±SD) was 172.2±46.8 days (FC-Patch Low) and 177.6±39.7 days (EVRA). Most subjects (>81%) were treated for 169-196 days. Average cycle length was 27.9±2.4 days (FC-Patch Low) and 27.9±25.days (EVRA). 4 subjects (1.9%) on FC-Patch Low and 32 subjects (2.5%) on EVRA had cycles longer than 28 days.

No deaths were reported. 411 treament-emergent (TE) AEs (TEAEs) in 174 subjects (43.7%) were reported (FC-Patch Low 47.5%; EVRA 39.9%). 185 TEAEs were study drug-related for 89 subjects (22.4%) with TEAEs (FC-Patch Low 24.0%; EVRA 20.7%). 26 subjects (6.5%) prematurely discontinued the study due to TEAEs (FC-Patch Low 9.0%, EVRA 4.0%), and none of the TEAEs causing discontinuation was serious. 6 subjects (1.5%) had TE-serious AEs (SAEs) and none of the SAEs was drug related: 2 subjects (1.0%) on FC-Patch Low for induced abortion and surgical removal of pre-existing lipoma, 4 subjects (2.0%) on EVRA for salpingo-oophoritis, gastroenteritis (2 subjects) and appendicitis. No SAEs were causally-related to the study medication and all recovered/resolved. 2 pretreatment pregnancies resulting in abortions (regarded as SAEs). 42 subjects (10.6%) had 57 pretreatment AEs, none related to protocol-required procedures.

TEAEs were most frequent in the following MedDRA System Organ Classess (SOC) with the corresponding MedDRA Preferred Terms: • Infections and infestations (FC-Patch Low 15.0%; EVRA 18.2%), mostly for nasopharyngitis (2.8%) and cystitis (2.8%); • General disorders and administrative site conditions (FC-Patch Low 19.5% and EVRA 11.1%), mostly for application site reaction (5.8%), application site pruritus (4.3%), and application site rash (2.3%); • Reproductive and breast disorders (FC-Patch Low 12.0%; EVRA 14.1%), mostly for metrorrhagia (4.3%), cervical dysplasia (4.5%), and breast pain (2.5%). Most frequent TEAEs (>3%) in the FC-Patch Low group were • application site reaction (7.5%), • cervical dysplasia (5.5%), • application site pruritus (5.5%), • metrorrhagia (4.5%); and in the EVRA group were • metrorrhagia (4.0%), • headache (4.0%), • application site reaction (4.0%), • breast pain (4.0%), • cervical dysplasia (3.5%), • cystitis (3.5%). Most frequent drug-related TEAEs (>3%) in the FC-Patch Low group were • application site reaction (7.5%), • application site pruritus (5.5%), • metrorrhagia (4.0%); and in the EVRA group were • metrorrhagia (4.0%), • application site reaction (4.0%), • breast pain (4.0%).

Premature discontinuations were more common for FC-Patch Low (9.0% of subjects) than EVRA (4.0%) and all but one (chest pain, FC-Patch Low) were drug-related. Most common drug-related TEAEs that led to discontinuation were General disorder and administration site conditions (e.g. application site reaction), and were more frequent for FC-Patch Low (8.5%) than EVRA (1.0%). Discontinuations for TEAEs in the SOC Reproductive system and breast disorders were reported only for EVRA (2.0%). TEAEs were almost all either mild or moderate in intensity. Severe TEAEs were rare (FC-Patch Low 2.0%; EVRA 1.0%). Most subjects recovered/resolved from their TEAEs (37.7% of 43.7% subjects with TEAEs).

Laboratory tests showed no adverse trends nor clinically meaningful changes from baseline. There were no concerns in abnormalities with liver function tests and lipid profile during the study, and most elevations/decreases either did not exceed 10% or were transient. The only exception was total bilirubin which decreased by 7% to 18% and stayed decreased at the final visit in both treatment groups. Except for 4 subjects (elevated triglycerides, elevated ASAT levels, decreased leukocytes, low potassium), all other clinically significant cases resolved (returned to normal) at subsequent visits. There were no clinically significant mean changes from baseline in vital signs, body weight or BMI, except for 2 subjects on EVRA with weight-related TEAEs (1 subject with weight fluctuations, another with a 12-kg weight increase who was withdrawn from the study; both recovered/resolved). Most subjects (89.7%) had normal cervical smear results at the end of the study. Of the 18 subjects (4.5%) with abnormal smear findings at the final examination (11 FC-Patch Low; 7 EVRA), 9 subsequently had normal smear results. The other 9 subjects (6 FC-Patch Low, 3 EVRA) had no further follow-up smears reported, and no data were available for 23 subjects (5.8%).

Results Summary — Pharmacokinetics

Covariate analysis revealed only body weight as a borderline statistically significant covariate on the clearance parameter of EE ($0.01 < p < 0.001$). Clearance values showed a log-linear increase with body weight within the range of this study (44-86kg). For a weight of 49kg (5th percentile) and 79.9kg (95th percentile), the clearance values were 91% and 113% of the typical value, respectively, based on median body weight. This suggests that the impact of body weight on clearance is limited and unlikely to be clinically relevant. In the combined PK/PD model for EE, GSD (PK) and SHBG (PD), no other statistically significant covariate influence was identified. Due to the influence of the serum concentrations of EE on the serum levels of SHBG and GSD, body weight had an indirect effect on both SHBG and GSD.

The effect of the patch application site (abdomen, arms or buttocks) on the PK of EE and GSD was also investigated. The release parameter was estimated to be 41% higher with FC-Patch Low applied to arm or buttocks than when applied on the abdomen. No application site effect could be established for EVRA in the model probably due the high variability of the EE PK. However, the geometric mean values of AUC(0 168)ss, Cav,ss and Cmax,ss suggest that EVRA has a similar application site effect. The estimated release parameter was higher by 1.9-fold (vs. FC-Patch Low on the arms and buttocks) to 2.6-fold (vs. FC-Patch low on the abdomen). For the combined model EE, GSD and SHBG for FC-Patch Low, no additional application site effects on the release were identified.

Results Summary — Other

Calculated overall compliance was similar in both groups (FAS 99.3%; PPS 99.9%). On average, subjects used 21.7±6.2 FC-Patch Low patches and 21.2±4.9 EVRA patches. Most subjects used exactly 3 patches per cycles (FC-Patch Low 62.0%; EVRA 70.1%). Patch application improved with time (i.e. exactly 3 patches were used by 66.8% of subjects in Cycle 1, and by 77.7% in Cycle 6). Unscheduled patch applications were mainly due to patches being detached for <24hours, either partially (FC-Patch Low 53.5%; EVRA 41.4%) or completely (FC Patch Low 39.0%; EVRA 27.3%). There were low rates of unscheduled applications due to patch detachments for ≥24hours (FC-Patch Low 3.5%; EVRA 7.1%) or skin reactions (FC Patch Low 7.0%; EVRA 6.6%). Detachments were documented as either partial/complete (FC-Patch Low 72.5%; EVRA 57.6%) or complete (FC-Patch Low 40.5%; EVRA 29.3%). Partial/complete patch detachments decreased with time (20.0% of subjects in Cycle 1; 15.7% in Cycle 6). There was no preferred application site for FC-Patch Low (abdomen 7.1±8.6 patches; arm 7.3±8.5 patches; buttocks 7.4±9.0 patches) but EVRA was applied more often on the buttocks (abdomen 5.3±7.4 patches; arm 6.1±7.8 patches; buttocks 9.8±9.4 patches). Partial/complete detachments were most frequent from the buttocks (FC-Patch Low 16.3% of patches; EVRA 8.7% of patches).

Overall satisfaction and convenience of use were generally well rated, and subjects were positive regarding certain qualities (e.g. contraception once a week, as reliable as the pill, low dose of hormones) and negative about others (e.g. edges of the patch became dirty or detached).

Conclusion(s)

The bleeding pattern and cycle control of FC-Patch Low and EVRA are similar. EE release rates for EVRA were 1.9 (on the arms and buttocks) to 2.6-fold (for the abdomen) higher compared to FC-Patch Low, but no application site effect was observed for GSD. More drug-related skin reactions were associated with FC-Patch Low than for EVRA. However, <9% of subjects dropped out due to these TEAEs and the overall dropout rate was similar between FC-Patch Low and EVRA (2.3% difference). The lower EE dose of FC-Patch Low had the advantage of fewer EE-related events (e.g. breast pain) which more frequently seen for EVRA. The AE profile was otherwise similar between the treatment groups. It can be concluded that FC-Patch Low is an efficacious and safe alternative to EVRA.

Date Created or Date Last Updated:	16 Dec 2013	**Date of Clinical Study Report:**	26 Oct 2011

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Appendix to Clinical Study Synopsis

Investigational Site List

Marketing Authorization Holder in Germany	
Name	**Bayer Vital GmbH**
Postal Address	**D-51368 Leverkusen** **Germany**
Sponsor in Germany (if applicable)	
Legal Entity Name	**Bayer Pharma AG**
Postal Address	**D-51368 Leverkusen** **Germany**

List of Investigational Sites

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3	Prof. Dr. J Huber	Allgemeines Krankenhaus der Stadt Wien Universitätskliniken	Währingergürtel 18-20	1090	Wien	Austria
4	Dr. H Kahr	Praxis Dr. Hannes Kahr	Glacisstrasse 35/1	8010	Graz	Austria
5	Dr. W Paulik	Dr. Walter Paulik	Aichfeldgasse 7	8740	Zeltweg	Austria
6	Dr. N Ruth	Praxis Dr. Norman Ruth	Giselastr. 2	6300	Wörgl	Austria
7	Dr. M Stiglbauer	Dr. Max Stiglbauer	Haggenmuellergasse 8	2700	Wiener Neustadt	Austria
8	Prof. Dr. W Urdl	Institut für Hormonstörungen und Kinderwunsch	Kaiser-Franz-Josef-Kai 46	8010	Graz	Austria
9	Prof. L Wildt	Universitätsklinikum Innsbruck	Anichstr. 35	6020	Innsbruck	Austria

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12	Dr. V Dvorak	Nestatni zdravotnicke zarizeni MUDr. Vladimir Dvorak	Orli 10	60200	Brno	Czech Republic
13	Dr. O Hlavackova	Gynekologicko-poradnicka ambulance Dr. Hlavackova	Zeyerova 2442	39701	Pisek	Czech Republic
14	Dr V Horejsi	Gynekologicka ambulance Vanda Horejsi, MD	Matice skolske 104/7	37001	Ceske Budejovice	Czech Republic
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16	Dr. I Kalousek	Medica s.r.o.Gynekologicko-porodnicke odd-leni Dr. Kalousek	Riegovo nam. 914	50002	Hradec Kralove	Czech Republic
17	MUDr. D Makalova	Femina Sana s.r.o	Perlitkova 1825/11	13000	Praha	Czech Republic
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