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:	15264	NCT01204190
Study Phase:	IIa	
Official Study Title:	Multicenter, open-label, randomized study to evaluate inhibition of ovulation during treatment with three transdermal patch formulations containing 0.55 mg ethinylestradiol (EE) and 2.10 mg gestodene (GSD) or 0.35 mg EE and 0.67 mg GSD or 0.275 mg EE and 1.05 mg GSD in healthy young female volunteers over a period of 3 treatment cycles	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Ethinlyestradiol (EE) and gestodene (GSD) patches (3 different patches containing different doses of EE and GSD)	
Name of Active Ingredient:	Ethinylestradiol and gestodene	
Dose and Mode of Administration:	The 3 different fertility-control patches contained the following doses of EE and GSD: • Treatment A: 0.55 mg EE + 2.1 mg GSD • Treatment B: 0.35 mg EE + 0.67 mg GSD • Treatment C: 0.275 mg EE + 1.05 mg GSD Route of administration for all patches: Transdermal (site: lower abdomen)	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Three treatment cycles (each treatment cycle comprising of 28 days: 21 patch-wearing days followed by 7 days patch-free interval)	
Studied period:	Date of first subjects' first visit:	28 SEP 2010
	Date of last subjects' last visit:	29 AUG 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	The study was conducted at one center in the Netherlands and one center in Germany.	
Methodology:	Subjects were randomized to receive one of the three treatments: Treatment A, B, or C after being stratified on the basis of body mass index (BMI) into two groups: BMI ≤30 kg/m^2 and >30 kg/m^2. The complete study comprised of four study periods: Screening, pre-treatment, treatment (treatment cycles 1, 2, and 3) and follow-up. The screening period started with the subject's signature on the informed consent form and ended when the subject was found to be	

	eligible for pre-dose assessment. The pre-treatment period comprised of 1 menstrual cycle, where the subjects underwent the baseline measurements. The treatment period comprised of the three treatment cycles and the accompanying study procedures. Assessments during the follow-up period were made at a single visit and comprised posttreatment examinations and controls as necessary. Ovarian activity during treatment cycles 2 and 3 was assessed on Days 3, 6, 9, 12, 15, 18, 21, 24, 26, 28 (transvaginal ultrasound [TVU], estradiol [E2] and progesteron serum concentrations)
Indication/ Main Inclusion Criteria:	Indication: Prevention of pregnancy Main Inclusion Criteria: Healthy female subjects, aged 18 – 35 years (smokers not older than 30 years, inclusive), ovulatory pre-treatment cycle
Study Objectives:	Primary: The primary objective of this study was to evaluate the inhibition of ovulation in treatment cycles 2 and 3 after dermal application of 3 different patch formulations containing EE + GSD for 3 treatment cycles. For the evaluation, ovarian activity was classified according to Hoogland and Skouby. Three parameters were combined to a 6-step scoring system: (a) the diameter of the maximum follicle like structure, (b) the estradiol (E2) serum concentration and (c) the progesterone serum concentration. Secondary: The following evaluations represented secondary objectives: • Levels of gonadotropins (FSH, LH) and ovarian steroids (E2, P) • Endometrial thickness • PK of EE, GSD and SHBG • Follicle size
Evaluation Criteria:	Efficacy (Primary): Not applicable Efficacy (Secondary): Not applicable Safety: Adverse events, including assessment of local tolerability; concomitant medication; vital signs (blood pressure and heart rate) and body weight; laboratory values; menstrual bleeding (diary).

	Pharmacodynamics Primary outcome measure • Hoogland score to evaluate the inhibition of ovulation: Ovarian activity during treatment cycles 2 and 3 was determined on the basis of follicle size measurements (by transvaginal ultrasound, TVU) and serum progesterone and estradiol concentrations (6-step grading of ovarian activity according to Hoogland). Secondary outcome measure • Blood level time course of gonadotropins i.e., follicle stimulating hormone (FSH) and luteinizing formone (LH) as well as steroid hormones estradiol and progesterone. • Follicle size and endometrial thickness measured by transvaginal ultrasound examination. Pharmacokinetics: Secondary outcome measure: Pharmacokinetics of EE, GSD, and sex hormone binding globulin (SHBG) • Analyses of EE, GSD and SHBG in serum once during pre-treatment and at selected time points during treatment cycles • Definition of a suitable structural PK model to characterize the PK of GSD and EE under consideration of SHBG in the three treatment groups. • Estimation of the population PK parameters and their associated precision and variability. • Estimation of interindividual variability in structural model parameters and residual variability between model-predicted and observed concentrations if appropriate. • Investigation of the potential influence of demographic and physiological covariates (e.g., age, body weight, body surface area) on the PK behavior of GSD and EE. Other: Patch adhesion (qualitative assessment and number of patches used).
Statistical Methods:	Demographic, safety, and pharmacokinetic data were described in summary tables and graphics. Efficacy (Primary): Not applicable Efficacy (Secondary): Not applicable Safety: Adverse events were summarized using MedDRA terms. Safety variables were analyzed by descriptive statistics, according to their type. For continuous safety variables, the change from baseline of the safety variable was also analyzed. Bleeding pattern and cycle-control variables were evaluated descriptively.

	Pharmacodynamics: The primary analysis was performed using a two-sided exact binomial 90% confidence interval, based on the Clopper-Pearson theory, for the proportion of subjects with ovulation in at least one of the treatment cycles 2 and 3 for each of the three treatments A, B, and C. As an additional analysis, the proportion of subjects with ovulation or luteinized unruptured follicle (LUF) was determined for each of the three treatments A, B, and C. Pharmacokinetics: The concentration–time courses of GSD, EE and SHBG in serum were summarized by treatment, cycle and additionally for the two BMI groups separately using descriptive statistics.
Number of Subjects:	Planned: Maximum 174 subjects randomized Analyzed: 173 subjects randomized, 171 treated (57 in the 0.55 mg EE + 2.1 mg GSD patch group, 57 in the 0.35 mg EE + 0.67 mg GSD patch group, and 57 in the 0.275 mg EE + 1.05 mg GSD patch group)

Study Results

Results Summary — Subject Disposition and Baseline

A total of 313 women were screened and, of these, 173 were randomized to receive one of the three study treatments. Two of these subjects were not treated. The remaining 171 received study treatment (57 subjects in each treatment group), and 153 completed treatment. The per protocol population (at least one application of study medication and no major protocol deviations), used for the primary pharmacodynamic analysis, numbered 152 subjects; the PK set (valid PK profile), the full analysis set (subjects treated and yielding at least one observation) and the safety set (all subjects treated) were identical, with 171 subjects.

Demographic and baseline data were comparable for all the three treatment groups. All subjects showed evidence of ovulation in the pre-treatment cycle, which was a condition for their remaining in the study and proceeding to the treatment cycles.

In total, 171 female subjects with an average age of 25.1 years (range: 18 to 35) were treated in the study. Their mean body mass index (BMI) was 26.3 kg/m^2 (range: 18.2 to 46.4). Of the 171 subjects, 120 (70%) had a BMI less than or equal to 30 kg/ m^2 and 51 (30%) had a BMI greater than this. Of the 171 subjects, 160 were White, 7 were Black or Afro-American, 2 were Asian, and 2 were of mixed race.

Results Summary — Safety

Numbers of patches worn and durations of patch-wearing corresponded well with the treatment stipulated in the study protocol. There was no major difference between the treatment groups in this respect.

There were no deaths in the study. There were two serious adverse events (pelvic pain caused by newly diagnosed endometriosis, in the treatment group "0.55 mg EE + 2.1 mg GSD", and pneumonia, in the "0.275 mg EE + 1.05 mg GSD") group. Neither was considered related to the study drug. These two events and a further 11 non-serious ones led to the withdrawal of a total of 12 subjects from treatment. The most frequent reason for withdrawal was application site reaction.

Overall, at least one treatment-emergent adverse event (TEAE) was recorded for 98% of subjects who received treatment. The most frequently occurring TEAEs were:

- Application site reaction (60% of the subjects: 61% treated with the 0.55 mg EE + 2.1 mg GSD patch, 63% treated with the 0.35 mg EE + 0.67 mg GSD patch and 56% treated with the 0.275 mg EE + 1.05 mg GSD patch.
- Nasopharyngitis (44% of the subjects: in the treatment groups, respectively, 42%, 47% and 42%)
- Headache (30% of the subjects: 35%, 25%, and 30%)
- Ovarian cyst (13% of the subjects: 0%, 18%, and 21%)
- Nausea (12% of the subjects: 14%, 16%, and 7%)
- Lower abdominal pain (12% of the subjects: 11%, 9%, and 16%)
- Influenza (12% subjects: 14%, 12%, and 9%)

The most frequently occurring adverse events considered related to the study treatment were:

- Overall 84% of the subjects (respectively, 84%, 82%, and 84% in each treatment group)
- Application-site reaction (58% of the subjects: 60%, 58%, and 56%)
- Headache (25% of the subjects: 26%, 25%, and 25%)
- Ovarian cyst (13% of the subjects: 0%, 18%, and 21%)
- Lower abdominal pain (12% of the subjects: 11%, 9%, and 16%)

Overall, the three different patches were well tolerated, without any apparent systematic differences between them in this respect.

Laboratory values gave results that were unremarkable, as did the measurements of vital signs and body weight (there was a single adverse event "weight increase" considered treatment-related).

Bleeding patterns were roughly comparable between the treatment groups. The treatment "0.55 mg EE + 2.1 mg GSD" (with the largest doses of EE and GSD) resulted in fewer spotting days than the other treatments did.

Results Summary — Pharmacodynamics

In the primary analysis, no subjects who wore the "0.55 mg EE + 2.1 mg GSD" patch showed ovulation in either of treatment cycles 2 or 3. In the other two treatment groups, several subjects showed ovulation. The respective percentages and 90% Clopper–Pearson confidence intervals were 0.0% [0.0%; 5.5%] for 0.55 mg EE + 2.1 mg GSD, 12.0% [5.4%; 22.3%] for 0.35 mg EE + 0.67 mg GSD, and 20.4% [11.5%; 32.2%] for 0.275 mg EE + 1.05 mg GSD.

Thus, the primary aim of the study – i.e., to show that the "0.55 mg EE + 2.1 mg GSD" patch provided adequate ovarian control and that the two lower-dose patches did not – was achieved.

Results were similar when treatment cycles 2 and 3 were examined separately. Similar results were also obtained for "ovulation or LUF", with no subjects in the "0.55 mg EE + 2.1 mg GSD" group showing ovulation/LUF and several subjects in each of the other groups showing this.

Hoogland scores also supported the above finding. Thus, in the treatment group "0.55 mg EE + 2.1 mg GSD", most subjects showed Hoogland 1 (no activity) in cycle 2; this was found for 64% of subjects overall, but for 20% or fewer in the lower-dose groups. The corresponding results for cycle 3 were similar.

The results on ovulation were supported by the results for FSH, LH, P and E2. Thus, antigonadotropic activity as monitored by FSH and LH was more effective among the subjects wearing the patch with the highest EE/GSD doses. Stronger suppression of ovarian activity by the highest EE/GSD patch formulation was demonstrated by comparison of progesterone and E2 serum concentrations as well as by monitoring of follicle growth. Maximum P values above 5 nmol/L (a level associated with follicle luteinization) were observed in the "0.55 mg EE + 2.1 mg GSD" treatment group for only a single subject, and only on three occasions in the first and second treatment cycles (follicle size <10 mm nevertheless implied a Hoogland score of 1). In the two lower-dose groups, P values of 40 to 50 nmol/L and more were observed. E2 values above 0.1 nmol/L, which indicate active follicle-like structures, were observed only for a small number of subjects in the "0.55 mg EE + 2.1 mg GSD" group, while this number was much greater in the lower-dose groups.

In the "0.55 mg EE + 2.1 mg GSD" group, all subjects had a maximum follicle size <13 mm in treatment cycles 1 and 2, with one subject above 13 mm (maximum follicle size above 20 mm). In the other two treatment groups, after treatment cycle 1 at least one-half of the group had a maximum follicle size above 13 mm.

The increase in endometrial thickness in a normal cycle was suppressed in all three treatment groups, albeit slightly more strongly in the "0.55 mg EE + 2.1 mg GSD" group.

In conclusion, the highest dose patch (0.55 mg EE + 2.1 mg GSD) gave rise to effective suppression of ovarian activity and reliable ovulation inhibition. These results were not obtained with the two patches containing respectively 0.35 mg EE + 0.67 mg GSD and 0.275 mg EE + 1.05 mg GSD.

Results Summary — Pharmacokinetics

Population PK models were established to investigate the PK of EE and of GSD after application of three different patches, the 0.55 mg EE + 2.1 mg GSD patch, the 0.35 mg EE + 0.67 mg GSD patch, and the 0.275 mg EE + 1.05 mg GSD patch. Because GSD elimination depends on SHBG, SHBG was also included in the model in order to adequately describe the PK of GSD. Covariate analysis on the PK behavior of EE revealed that body weight has a statistically significant influence on the clearance parameter of EE, although the impact of body weight on clearance was limited and is not considered to be clinically relevant. The clearance values showed a log-linear increase with body weight within the range of this study (46.2 – 134 kg, N=171). Using the 5^{th} and 95^{th} percentiles of the observed body weight distribution which correspond to 52.4 kg and 107 kg, the clearance values were 88.7% and 118% of the typical value, respectively, based on the median body weight (68.8 kg). 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. No additional covariate effect was found in the present study.

The final population PK model for EE, GSD and SHBG was then used to estimate the area under the drug concentration-time curve (AUC(0–168)), the average concentration (C_{av}), and maximum drug concentration (C_{max}) values for the first, second, and third week (w3) of the third treatment cycle for all subjects included in the evaluation. Unbound GSD concentrations were calculated by using total GSD concentrations and the fraction unbound as provided by the model. The geometric mean PK parameter values (AUC(0–168)) w3 for EE, total, and unbound GSD as well as C_{av} w3 for SHBG) estimated based on the final population PK model EE/SHBG/GSD for the third week of the third treatment cycle for the 0.55 mg EE + 2.1 mg GSD patch, the 0.35 mg EE + 0.67 mg GSD patch, and the 0.275 mg EE + 1.05 mg GSD patch are summarized (geometric coefficient of variation in parentheses) in Table 1.

Table 1: Geometric mean PK parameter values of EE, SHBG, total and unbound GSD estimated based on the final population PK model EE/SHBG/GSD for the third week of the third treatment cycle for all 171 subjects (geometric coefficient of variation (%) in parenthesis)

Analyte	Parameter	Unit	0.55 mg EE + 2.1 mg GSD patch	0.35 mg EE + 0.67 mg GSD patch	0.275 mg EE + 1.05 mg GSD patch
EE	AUC(0–168) w3	(ng*h)/L	4774 (25.2%)	3930 (20.9%)	2261 (28.7%)
	C_{av} w3	ng/L	28.4 (25.2%)	23.4 (20.9%)	13.5 (28.7%)
	C_{max} w3	ng/L	41.6 (18.3%)	33.6 (15.1%)	18.6 (21.3%)
GSD total	AUC(0–168) w3	(µg*h)/L	645 (50.4%)	274 (52.5%)	233 (62.2%)
	C_{av} w3	µg/L	3.84 (50.4%)	1.63 (52.5%)	1.39 (62.2%)
	C_{max} w3	µg/L	4.86 (47.5%)	2.07 (52.3%)	1.82 (62.5%)
GSD unbound	AUC(0–168) w3	(µg*h)/L	4.96 (32.2%)	2.06 (35.0%)	2.10 (39.4%)
	C_{av} w3	µg/L	0.0296 (32.2%)	0.0123 (35.0%)	0.0125 (39.4%)
	C_{max} w3	µg/L	0.0383 (30.6%)	0.0159 (35.9%)	0.0168 (40.6%)
SHBG	C_{av} w3	nmol/L	188 (35.0%)	188 (35.5%)	145 (38.4%)

The following parameter descriptions are used in the PK/PD Evaluation Report (A58794): AUC(0–168) w3 = AUCTAU(336-504), C_{av} w3 = CAV(336-504), C_{max} w3 = CMAX(336-504)

Comparison of the geometric means of the AUC(0–168) week 3 values showed that the EE exposure after treatment with the 0.35 mg EE + 0.67 mg GSD patch is 17.7% lower than the 0.55 mg EE + 2.1 mg GSD patch. The EE exposure of the 0.275 mg EE + 1.05 mg GSD patch was as expected; approximately half the exposure of the 0.55 mg EE + 2.1 mg GSD patch. Comparison of the geometric means of AUC(0–168) w3 values for unbound GSD showed that the exposure after treatment with the 0.275 mg EE + 1.05 mg GSD patch as well as after treatment with the 0.35 mg EE + 0.67 mg GSD patch was slightly less than half of the value for the 0.55 mg EE + 2.1 mg GSD patch. The effect on the unbound GSD exposure was more pronounced than expected by the reduction in size and therefore drug content by 50% which is probably due to the nonlinear (Michaelis-Menten) elimination of GSD.

Results Summary — Other

Patch adhesion: Approximately 30% of the subjects used more than the 3 planned patches per cycle.

Conclusion(s)

In this study of 173 subjects, the three different patches, applied for three treatment cycles, were well tolerated. No major difference was seen between the three treatments in terms of safety or tolerability of the patches, except for ovarian cyst which occurred more frequently with the 0.35 mg EE + 0.67 mg GSD patch and the 0.275 mg EE + 1.05 mg GSD patch. With the 0.55 mg EE + 2.1 mg GSD patch, suppression of ovarian activity and, thereby, reliable inhibition of ovulation were demonstrated. In accordance with the approximately half-reduced exposure of unbound GSD and the not or half-reduced EE exposure, reliable suppression of ovarian activity was not achieved in all subjects with the 0.35 mg EE + 0.67 mg GSD patch and the 0.275 mg EE + 1.05 mg GSD patch. Cycle control was judged as good in all treatment groups but was best in the 0.55 mg EE + 2.1 mg GSD patch group.

The 0.275 mg EE + 1.05 mg GSD patch, which had half the size and dose compared with the patch under development (the 0.55 mg EE + 2.1 mg GSD patch), led as expected to approximately 50% of the EE exposure and approximately 50% (slightly less) of the unbound GSD exposure. The EE exposure during wearing off of the 0.35 mg EE + 0.67 mg GSD patch was close to that from the 0.55 mg EE + 2.1 mg GSD patch, and the unbound GSD exposure was approximately 50% (or slightly less) of that from the 0.55 mg EE + 2.1 mg GSD patch, which was also in line with expectation. The population PK evaluation showed only a small influence of body weight on the pharmacokinetics of EE that is unlikely to be of clinical relevance. With regard to body weight, the clearance of EE varied between 88.7% and 118% of the typical value in the range of 52.4 kg to 107 kg. An additional effect, beside the indirect effect through EE and ultimately SHBG, was not observed for GSD.

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