Clinical Study Synopsis

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Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	14348	NCT00915915
Study Phase:	II	
Official Study Title:	Multicenter, open-label, randomized study to evaluate inhibition of ovulation of two transdermal patch formulations containing 0.55 mg ethinylestradiol (EE) and either 1.05 or 2.1 mg gestodene (GSD) in healthy young female volunteers over a period of 3 treatment cycles	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Gestodene/EE Patch (BAY86-5016), Transdermal Patch	
Name of Active Ingredient:	Ethinylestradiol and gestodene	
Dose and Mode of Administration:	Treatment A: 0.55 mg EE + 2.1 mg GSD per patch Treatment B: 0.55 mg EE + 1.05 mg GSD per patch Mode of administration: Transdermal (site: lower abdomen)	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Three treatment cycles, 7 days per patch; 21 days per treatment cycle, i.e., 3 x 7 days patch-wearing phase and a patch-free interval of 7 days	
Studied period:	Date of first subjects' first visit:	15 JUN 2009
	Date of last subjects' last visit:	07 APR 2010
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	This study was conducted at two centers in Germany	
Methodology:	This was a 2-arm design study with 1 pre-treatment cycle, 3 treatment cycles, and 1 follow-up cycle. The complete study comprised of four study phases: Screening, predose, treatment (treatment cycles 1, 2, and 3) and follow-up. Ovarian activity during treatment cycles 2 and 3 was determined based on follicle size measurements (by transvaginal ultrasound, TVU) and serum progesterone and estradiol concentrations (6-step grading of ovarian activity according to Hoogland [Hoogland HJ, Skouby SO: Ultrasound evaluation of ovarian activity under oral contraceptives, Contraception 1993, 47 : 583-590]). Cervical effects (Insler Score) for determination of hormonal effects on the cervix and the cervical mucus were analysed during pre-treatment cycle and treatment cycle 3. Blood sampling for analysis of EE, GSD and sex hormone-binding globulin	

	serum (SHBG) were taken at pre-dose and during the 2nd and 3rd treatment cycles.
Indication/ Main Inclusion Criteria:	Indication: Prevention of pregnancy Inclusion criteria: Healthy female subjects, aged 18 – 35 years (smoker not older than 30 years, inclusive), ovulatory pre-treatment cycle.
Study Objectives:	Primary: To evaluate the inhibition of ovulation in treatment cycles 2 and 3 after administration of two different patches containing EE and GSD for 3 treatment cycles. Secondary: • To evaluate the inhibition of ovulation in treatment cycles 2 and 3 after administration of two different patches containing EE and GSD for 3 treatment cycles. • To evaluate the ovarian activity in treatment cycles 2 and 3 (Hoogland Score). • To evaluate the course of gonadotropins (follicle-stimulating hormone, luteinizing hormone), progesterone and estradiol. • To evaluate the endometrial thickness. • To evaluate follicle size. • To evaluate cervical effects (Insler Score) for determination of the hormonal effects on the cervix and the cervical mucus in pre-treatment cycle and treatment cycle 3. • To evaluate the pharmacokinetics of EE, GSD and sex hormone-binding globulin in treatment cycles 2 and 3. • To evaluate the proof of ovulation in the follow-up cycle.
Evaluation Criteria:	Efficacy (Primary): Proportion of subjects with ovulation in at least one of the treatment cycles 2 and 3 (primary variable). Efficacy (Secondary): Not applicable Safety: Secondary variables: • Course of gonadotropins (FSH, LH, P, E2) • Endometrial thickness and follicle size • Cervical effects (Insler score) for determination of hormonal effects on cervix and the cervical mucus during pretreatment cycle and treatment cycle 3 • Pharmacokinetics of EE, GSD, and SHBG in treatment cycles 2 and 3 Other safety variables: Blood pressure, heart rate, body weight, safety laboratory values and assessment of values, urine pregnancy test, bleeding intensity, adverse events and concomitant medication.

	Pharmacokinetics: Non-compartmental and population pharmacokinetic analyses, concentration-time courses of EE, GSD and SHBG, pharmacokinetic parameters. Other: Patch adhesion was evaluated by number of subjects using more than 3 planned patches per cycle.
Statistical Methods:	Efficacy (Primary): The primary variable proportion of subjects with ovulation (i.e., Hoogland score 6) in at least one of the treatment cycles 2 and 3 was analyzed by summary tables were calculated for each treatment arm. Two-sided exact binomial 90% confidence intervals, based on the Clopper-Pearson theory, were also calculated for each treatment arm. Efficacy (Secondary): Not applicable Safety: Safety data was described in summary tables and graphics.
	Pharmacokinetics: Pharmacokinetic data was described in summary tables and graphics. Other: No statistical comparisons were planned for patch adhesion.
Number of Subjects:	Planned: 100 (50 per treatment) Analyzed: 108 treated (55 in 0.55 mg EE/1.05 mg GSD patch group and 53 in 0.55 mg EE/2.1 mg GSD patch group)

Study Results

Results Summary — Subject Disposition and Baseline

A total of 197 female subjects were screened, and 110 subjects were randomized. A total of 108 Caucasian female subjects with an average age of 27.9 years (range: 18 to 35 years) and average body mass index (BMI) of 22.1 Kg/m^2 (range: 18.1 – 29.7 Kg/m^2) were treated at least once in the study and were therefore valid of the safety analysis. Of these, 92 subjects (N=48 with 0.55 mg EE/1.05 mg GSD Patch and N = 44 with 0.55 mg EE/2.1 mg GSD Patch) completed the study at 2 centers and were valid for the per-protocol analysis.

For population pharmacokinetic approach, the full analysis set was used including 99 subjects (50 in the 0.55 mg EE/1.05 mg GSD patch group and 49 in the 0.55 mg EE/2.1 mg GSD patch group) who received at least one application of study medication and had at least one valid measurement of the Hoogland score in one of the treatment cycles. Sixty-five subjects who did not replace the worn patch during the respective week were included in the non-compartmental pharmacokinetic evaluation.

Results Summary — Efficacy

Ovulation was not detected for any of the 92 subjects valid for per-protocol analysis (i.e., Hoogland score=6) in treatment cycles 2 and 3, which was in accordance with the similar drug exposures observed for both patches.

The growth pattern of maximum follicle size during the menstrual cycle was suppressed in both treatment groups. While the mean maximum follicle sizes by most subjects were reached on cycle day 15 (all subjects in the 0.55 mg EE/1.05 mg GSD patch group) and on day 12 (42 of 44 in the 0.55 mg EE/2.1 mg GSD patch group) in the pre-treatment cycles, no mid-cycle cluster of maximum follicle size days was observed under treatment in both groups. The largest follicles were seen at the beginning of the cycle due to the absence of the inhibition of the pituitary gland and the ovary during the patch-free interval.

The incidence of maximal cervical score rating in the pre-treatment cycle for slight (scores 4 - 6) was 4% with the 0.55 mg EE/1.05 mg GSD patch group and 7% with the 0.55 mg EE/2.1 mg GSD patch group, for moderate (scores 7 - 9) 35% with the 0.55 mg EE/1.05 mg GSD patch group and 30% with the 0.55 mg EE/2.1 mg GSD patch group, and for full (scores 10 - 12) 60% with the 0.55 mg EE/1.05 mg GSD patch group and 64% with the 0.55 mg EE/2.1 mg GSD patch group.

Based on cycle days during the complete treatment cycle 3 for most of the subjects, a cervical score rating slight (scores 4 - 6) or negative (scores 0 - 3) was observed.

The incidence of maximal cervical rating in treatment cycle 3 for slight (scores 4 - 6) was 40% with the 0.55 mg EE/1.05 mg GSD patch group and 32% with the 0.55 mg EE/2.1 mg GSD patch group, for moderate (scores 7 - 9) 46% with the 0.55 mg EE/1.05 mg GSD patch group and 57% with the 0.55 mg EE/2.1 mg GSD patch group. Only 4 subjects (8%) had a maximal cervical score rating full (scores 10 - 12) with the 0.55 mg EE/1.05 mg GSD patch group and no subject with the 0.55 mg EE/2.1 mg GSD patch group.

No mid-cycle change could be evaluated. This is in line with the high proportion of subjects with a Hoogland Score 1 and predominant rate of follicle size ≤10 mm for all treatment cycles.

As compared to the pre-treatment cycle mean and median values of the gonadotropins, FSH and LH during treatment for both patches were clearly lower at the time interval when a peak was to be expected (mid-cycle peak). In no case, could a mean LH peak be clearly detected after the start of study drug administration, whereas values up to 20 U/L were measured in the untreated cycle.

The increase in mean progesterone up to values about 41 nmol/L during the second half of the pre-treatment cycle was suppressed in both treatment groups.

Mean estradiol values were clearly decreased by both patches in comparison to the pre-treatment cycle. All mean E2 values observed during treatment were below 0.1 nmol/L in both patch groups.

The normal pattern of endometrial growth that had been observed in the pre-treatment cycle was suppressed from the first treatment cycle onwards in both treatment groups. Endometrial thickness remained at the same level of approximately 3 - 6 mm for all treatment cycles. Without treatment, mean values up to 9 mm were reached by day 24. However, treatment with EE/GSD clearly reduced endometrial thickness. There was no clear difference observed between the two treatment groups.

Results Summary — Safety

No deaths occurred during this study. Two serious adverse events (SAEs) occurred during the treatment phase: otosclerosis (study drug-related) and appendicitis (not study drug-related). In addition to the 2 subjects with SAEs, four other subjects withdrew from the study prematurely due to adverse events (AEs): application site-reaction (study drug-related), migraine (study drug-related), abnormal thyroidal laboratory parameters (not study drug-related) and elevated dehydroepiandrosterone sulfate (DHEA-S) (not study drug-related).

In total, 106 out of the 108 subjects who received treatment had at least one treatment-emergent AE.

The most frequently occurring treatment-emergent AEs were

- Application site-reaction (50 subjects: 26 with 0.55 mg EE/1.05 mg GSD patch and 24 with 0.55 mg EE/2.1 mg GSD patch),
- Nasopharyngitis (47 subjects: 19 with 0.55 mg EE/1.05 mg GSD patch and 28 with 0.55 mg EE/2.1 mg GSD patch),
- Headache (28 subjects: 17 with 0.55 mg EE/1.05 mg GSD patch and 11 with 0.55 mg EE/2.1 mg GSD patch),
- Red blood cell count decreased (19 subjects: 12 with 0.55 mg EE/1.05 mg GSD patch and 7 with 0.55 mg EE/2.1 mg GSD patch).

Of these, 85 subjects experienced treatment-emergent AEs, which were assessed as being related to the study drug: 46 subjects with 0.55 mg EE/1.05 mg GSD patch and 39 subjects with 0.55 mg EE/2.1 mg GSD patch.

The most frequently occurring related treatment-emergent AEs were:

- Application site-reaction (50 subjects: 26 with 0.55 mg EE/1.05 mg GSD patch and 24 with 0.55 mg EE/2.1 mg GSD patch),
- Headache (20 subjects: 12 with 0.55 mg EE/1.05 mg GSD patch and 8 with 0.55 mg EE/2.1 mg GSD patch),
- Breast discomfort (14 subjects: 10 with 0.55 mg EE/1.05 mg GSD patch and 4 with 0.55 mg EE/2.1 mg GSD patch),
- Acne (12 subjects: 8 with 0.55 mg EE/1.05 mg GSD patch and 4 with 0.55 mg EE/2.1 mg GSD patch).

The two different patches were well tolerated. No clinically relevant difference could be seen between the two treatments.

Regarding vital signs, there were no clinically relevant changes observed in any subject. A very slight decrease in mean body weight over time could be seen with 0.55 mg EE/2.1 mg GSD (maximum mean change -0.439 kg), whereas mean body weight very slightly increased with 0.55 mg EE/1.05 mg GSD (maximum mean change +0.741 kg).

Results regarding bleeding pattern were similar for the 2 different treatment groups:

- Intracyclic bleeding decreased from cycle 1 to cycle 3 in both patch groups. Intracyclic bleeding events after the first treatment cycle were only observed in single subject in both treatment groups. The main intensity for most of the subjects was spotting, except in treatment cycle 3 for the 0.55 mg EE/2.1 mg GSD patch group slight bleeding was observed in 50% of the subjects.
- Withdrawal bleeding was present in more than 80% of the subjects, who mainly reported bleeding of normal intensity. Based on these data cycle control may be judged as acceptable.

Pharmacokinetic concentrations of EE, GSD and SHBG were determined at pre-dose and regularly during cycles 2 and 3. Pharmacokinetic parameters of EE, total and unbound GSD as well as SHBG were specifically determined for the third week during treatment cycle 3 as representative steady-state parameters for all investigated analytes. In the present study, the non-compartmental analysis was planned to provide early data on the exposure of EE and GSD. Using non-compartmental analysis methods, pharmacokinetic (PK) parameters for EE and total GSD were calculated in a subgroup of 65 subjects. Based on serum concentration data in 99 subjects, a population PK analysis was performed as the main pharmacokinetic analysis. Based on the final model, individual PK parameters of EE, total and unbound GSD as well SHBG were estimated for all evaluable subjects.

The geometric mean pharmacokinetic parameters and geometric coefficients of variation in parentheses are based on the population pharmacokinetic evaluation and are summarized in Table 1.

Table 1: Geometric mean PK parameters of EE, SHBG, total and unbound GSD estimated based on the final population PK model for the third week of the third treatment cycle in 99 subjects

Analyte	Parameter	Unit	EE/GSD (0.55 mg/1.05 mg) Patch	EE/GSD (0.55 mg/2.1 mg) Patch
EE	$AUC(0\text{-}168)_{ss}$	ng*h/L	5368 (29.1%)	4011 (26.3%)
	$C_{av,ss}$	ng/L	31.9 (29.1%)	23.9 (26.3%)
	$C_{max,ss}$	ng/L	46.9 (33.5%)	32.8 (27.8%)
GSD total	$AUC(0\text{-}168)_{ss}$	µg*h/L	627 (36.5%)	687 (37.0%)
	$C_{av,ss}$	µg/L	3.73 (36.6%)	4.09 (37.0%)
	$C_{max,ss}$	µg/L	4.60 (33.1%)	5.27 (33.6%)
GSD unbound	$AUC(0\text{-}168)_{ss}$	µg*h/L	3.68 (27.4%)	5.06 (26.4%)
	$C_{av,ss}$	µg/L	0.0219 (27.4%)	0.0301 (26.4%)
	$C_{max,ss}$	µg/L	0.0273 (23.3%)	0.0395 (22.4%)
SHBG	$C_{av,ss}$	nmol/L	265 (26.1%)	201 (25.1%)

The model-based mean $C_{max,ss}$ and $AUC(0\text{-}168)_{ss}$ values of EE were always higher for the 0.55 mg EE/1.05 mg GSD patch in comparison with the 0.55 mg EE/2.1 mg GSD patch resulting in 1.3-fold higher serum concentrations of EE during treatment with the patch containing half the GSD amount.

In accordance with the higher EE serum concentration for the 0.55 mg EE/1.05 mg GSD patch, the mean SHBG concentrations during week 3 of cycle 3 were about 1.3 times higher than those of the 0.55 mg EE/2.1 mg GSD patch.

The pharmacokinetic parameters of total GSD were very similar for both patches; however, due to the different SHBG concentration, the pharmacokinetic parameters of unbound GSD are more relevant. The mean $C_{max,ss}$ and $AUC(0\text{-}168)_{ss}$ values of unbound GSD after application of the patch containing half the GSD amount were 0.7 times of those observed after full dose patch.

The pharmacokinetic data clearly indicate that the relative amount of EE and GSD delivered from the 0.55 mg EE/1.05 mg GSD patch were clearly higher in comparison with the 0.55 mg EE/2.1 mg GSD patch.

Results Summary — Other
Regarding patch adhesion, up to approximately 30% of the subjects used more than the 3 planned patches per cycle.

Conclusion(s)

Based on the results of this study of 108 subjects, the application of the two different patches containing similar EE amounts but different GSD amounts was well tolerated over 3 treatment cycles. No major difference was seen between the two treatments. The frequency and type of adverse events do not differ from those expected after oral administration of the two hormones.

With both patches, similar suppression of ovarian activity and, thereby, reliable ovulation inhibition was demonstrated. In both treatment groups, cycle control was judged as acceptable.

The pharmacokinetic data showed an unexpectedly high release of both active components of the 0.55 mg EE/1.05 mg GSD patch. According to these data, the delivered dose of GSD which became systemically available as unbound GSD was only 30% lower for the patch containing half the GSD amount. On the other hand, the amount of EE delivered from this patch was approximately 30% higher in comparison with 0.55 mg EE/2.1 mg GSD patch. Thus, the pharmacokinetic data clearly supports the observed similarity of the pharmacodynamic results of the two patches.

Since the 0.55 mg EE/1.05 mg GSD patch did not deliver the expected doses of GSD and EE, the aim of the present study to demonstrate sufficient ovarian suppression at lower doses could not be achieved.

Publication(s):	None		
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