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:	91558	NCT00729404
Study Phase:	IIa	
Official Study Title:	Multicenter, open-label, randomized study to evaluate inhibition of ovulation of two transdermal patch formulations containing 0.55 mg ethinylestradiol and either 1.05 or 2.1 mg gestodene 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 (EE), gestodene (GSD)	
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:	Each of the treatments was to be administered for 3 treatment cycles. During each treatment cycle, the patch was to be worn for 3 consecutive weeks (21 days) followed by a 7-day patch free interval.	
Studied period:	Date of first subjects' first visit:	27 AUG 2008
	Date of last subjects' last visit:	19 FEB 2009
Premature Study Suspension / Termination:	The study was prematurely terminated on 09 FEB 2009. The study was prematurely discontinued as the standard genotoxicological investigations with the investigational medicinal product used in this study revealed a weakly positive effect in a mouse lymphoma assay (described in the Notification of an Unexpected Adverse Effect from Nonclinical Drug Safety, dated 11 NOV 2008). The toxicological significance of this safety related observation was needed to be clarified in additional preclinical studies. Due to this issue, a risk benefit assessment was performed. As healthy young female volunteers were to be included in the study and the contraceptive efficacy of the investigational medicinal product was not yet proven, no benefit for the subjects could be expected. Therefore, even a possible slight increase of a risk to their health was taken seriously. The likelihood of adverse health effects in women already treated with this patch was assessed as rather low in the Nonclinical Expert Statement.	

	Nevertheless, it was decided to stop the study immediately; and the study was put on hold on 12 NOV 2008. All subjects terminated their patch administration. The planned follow-up examinations were performed. On 09 FEB 2009, it was determined that the weakly positive effect in the toxicological test was not confirmed by the extensive follow-up testing and was therefore considered not relevant to the *in vivo* situation. Therefore, on 09 FEB 2009, it was decided to discontinue the study officially and to start a new study.
Substantial Study Protocol Amendments:	None
Study Centre(s):	The study was conducted at 2 centers in Germany.
Methodology:	In this study, subjects were randomized to one of the two treatment groups (i.e, Treatment A or B). The study comprised of four study periods in total: Screening, pre-dose, treatment (treatment cycle 1, 2 and 3) and follow-up. The screening period started with the subject's signature on the informed consent form and ended with the eligibility for pre-dose assessment. During the pre-dose, the subjects underwent baseline measurements, especially for the proof of ovulation. The treatment period comprised of 3 treatment cycles, where the measures to fulfill the study objectives were performed. The follow-up period consisted of post-treatment examinations including controls, if necessary. The study was performed on an outpatient basis, monitoring the subjects regularly for adverse events (AEs) and concomitant medications. The subjects' uterus with cervix and endometrium, both ovaries, and Douglas' pouch (excavatio recto-uterina) were required to be examined at every visit. The diameter of the largest follicle-like structure and endometrial thickness was required to be measured at different time points throughout the study. Blood samples for the determination of estradiol (E2), progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) in serum were to be taken at every visit during the pre-treatment cycle and the treatment cycles except for the days in treatment cycle 3 where only pharmacokinetic samples were withdrawn.
Indication/ Main Inclusion Criteria:	Indication: Prevention of pregnancy Main inclusion criteria: Healthy female volunteers, aged 18 – 35 years (smoker not older than 30 years, inclusive), ovulatory pre-treatment cycle.
Study Objectives:	<u>Overall:</u> • To evaluate the inhibition of ovulation in treatment cycles 2 and 3 after dermal administration of two different patches containing EE and GSD for 3 treatment cycles. • To assess ovarian activity in treatment cycles 2 and 3 (Hoogland Score). • To evaluate the course of gonadotropins (FSH, LH), progesterone (P) and E2. • To evaluate endometrial thickness. • To evaluate follicle size. • To evaluate the pharmacokinetics of EE, GSD and sex hormone-binding globulin (SHBG) in treatment cycles 2 and 3.

	Primary: Not Applicable Secondary: Not Applicable
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was planned to be the proportion of subjects with ovulation in at least one of the treatment cycles 2 and 3. Efficacy (Secondary): The secondary efficacy variables planned were: • Assessment of ovarian activity during treatment cycles 2 and 3 (Hoogland score) • Course of gonadotropins (FSH, LH, P, E2) • Endometrial thickness • Follicle size Safety: Screening examinations, laboratory examinations, AEs
	Pharmacokinetics: Planned: Analyses of EE, GSD and SHBG in serum during pre-treatment and the 2nd and 3rd treatment cycles
Statistical Methods:	Efficacy (Primary): Descriptive statistics were to be used. The primary analysis was planned to be performed using a two-sided exact binomial 90% confidence interval, based on the Clopper-Pearson theory, for the proportion of subjects with Hoogland score 6 (i.e., ovulation) in at least one of the treatment cycles 2 and 3 for each of the two treatment groups. Efficacy (Secondary): The secondary analysis was also planned to be performed using a two-sided exact binomial 90% Clopper-Pearson confidence interval, for the proportion of subjects with Hoogland score 6 calculated for the treatment cycles 2 and 3 for each of the two treatment groups. Safety: Safety variables were analyzed with descriptive statistics, according to their type. For all safety analyses, the safety analysis set (SAF) population was used. All treatment-emergent adverse events were presented in frequency tables for both subject count ("number of subject reporting adverse event") and event count ("number of reported adverse events"). The frequency tables were based on classified data, and the classification was done according to Medical Dictionary for Regulatory Activities (MedDRA) coding system. The AE intensity and relationship to study drug, specific drug and non-drug treatment, seriousness, and outcome were presented by data listings and appropriate frequency tabulations.

	Pharmacokinetics : Individual and mean plasma-concentration vs time curves were plotted by treatment and cycle using both linear and semilogarithmic scales. Pharmacokinetic parameters were summarized using descriptive statistics.
Number of Subjects:	Planned: 50 subjects per treatment (up to a maximum of 58): Total = 100 subjects (maximum 116) Analyzed: Randomized: 8 and 9 subjects per treatment: Total = 17, treated: 6 and 7 per treatment: Total = 13 subjects

Study Results

Results Summary — Subject Disposition and Baseline

A total of 208 subjects were screened, but only 17 subjects were randomized due to the premature discontinuation of the study. At the time the study was stopped (put on hold on 12 NOV 2008), a total of 13 subjects (7 subjects with 0.55 mg EE/1.05 mg GSD patch and 6 subjects with 0.55mg EE/2.1 mg GSD patch) had started patch administration. The maximum treatment period was 2 weeks (First Patient First Treatment was on 28 OCT 2008).

Results Summary — Efficacy

Due to the premature discontinuation of the study, insufficient data were obtained to perform the planned efficacy analysis.

Results Summary — Safety

No deaths or serious or significant AEs were reported. Six out of 13 subjects experienced at least one treatment-emergent AE. In total, 18 treatment-emergent AEs were documented (13 events in 4 subjects with 0.55mg EE/1.05 mg GSD patch and 5 events in 2 subjects with 0.55mg EE/2.1 mg GSD patch). The most frequent events were serum ferritin decreased (3 events in 3 subjects: 2 with 0.55mg EE/1.05 mg GSD patch and 1 with 0.55mg EE/2.1 mg GSD patch) and headache (2 events in 2 subjects: both with 0.55mg EE/2.1 mg GSD patch). Only 1 subject had an AE which was assessed as being related (drug exposure during pregnancy).

There were no clinically relevant changes or trends observed for any of the laboratory parameters nor for the vital sign measurements.

Results Summary — Pharmacokinetics

Due to the premature discontinuation of the study, blood samples for the pharmacokinetic analysis were not obtained; therefore, the planned pharmacokinetic analysis described was not done.

Conclusion(s)

Due to the early discontinuation of this study, there was not sufficient data available to perform the planned efficacy/pharmacodynamic analysis nor the planned pharmacokinetic analysis. Both patch treatments were well tolerated by all the subjects.

Publication(s):	None		
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