Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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:	91697 (311623)	NCT00631124
Study Phase:	IIa	
Official Study Title:	A double-blind, randomized, uncontrolled study to evaluate inhibition of ovulation of two oral estradiol/drospirenone regimens in healthy young female volunteers over a period of 3 treatment cycles	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	E2/DRSP (1 - 2 mg/2 - 3 mg) (BAY 86-4891)	
Name of Active Ingredient:	Estradiol (E2), drospirenone (DRSP)	
Dose and Mode of Administration:	The test product was administered orally as a monophasic regimen with E2 and DRSP, and a triphasic regimen with E2 and DRSP. Treatment A, monophasic regimen Day 1 - 24: 1.5 mg E2 + 3 mg DRSP (SH T04984E) Day 25 - 26: placebo (SH T04984PE) Day 27: 3 mg DRSP (SH T04984F) Day 28: placebo (SH T04984PE) Treatment B, triphasic regimen Day 1 - 8: 1 mg E2 + 3 mg DRSP (80458739) Day 9 - 16: 1.5 mg E2 + 2.5 mg DRSP (80458720) Day 17 - 24: 2 mg E2 + 2 mg DRSP (80458712) Day 25 - 28: placebo (SH T04984PE)	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Three treatment cycles, i.e., 3 x 28 days = 84 days in total; 1 tablet per day.	
Studied period:	Date of first subjects' first visit:	04 FEB 2008
	Date of last subjects' last visit:	09 DEC 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	The study was conducted at two centers in Germany.	
Methodology:	The study comprised of a total of 4 study periods: Screening, pre-dose (pre-treatment cycle), treatment, and follow-up phase. The screening period started with the subjects' signature on the informed consent form and ended with the eligibility for pre-dose assessment. During pre-dose, the subjects underwent baseline measurements, especially	

	for proof of ovulation. The subjects were randomized to treatment A or treatment B and treatment was administered over 3 treatment cycles. The treatment period comprised of the 3 treatment cycles, where the measures to fulfill the study objectives were performed. Clinical visits were performed every sixth day during treatment cycle 1 and every third day during cycles 2 and 3. Measurements during the follow-up period consisted of post-treatment examinations including controls, if necessary. The study was performed on an outpatient basis. Diary entries (bleeding intensity) were done on a daily basis by the subject, starting with the first day of menstrual bleeding. Transvaginal ultrasound (TVU) was done at each visit of all treatment cycles by a physician. Blood sampling for (progesterone, LH [Luteinizing hormone], Follicle-stimulating hormone [FSH]) was done at each visit in all the treatment cycles. Additionally for treatment cycle 3, blood sampling for estrone (E1), E2, DRSP was done for pharmacokinetic (PK) analysis. Scoring of ovarian activity according to Hoogland was done by an investigator on day 28 at the earliest (or when the results of progesterone concentration measurements became available) for treatment cycles 2 and 3. The observation phases for adverse events (AEs) started with the first study drug administration on day 1 of the 1st treatment cycle, and ended with the last follow-up visit for the follow-up period.
Indication/ Main Inclusion Criteria:	Indication: Female contraception Main Inclusion Criteria: Healthy female subjects, aged 18 – 35 years (smokers 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 (one mono- and one triphasic) 24-day regimens containing E2 and DRSP for 3 treatment cycles. Secondary: • Assessment of ovarian activity in treatment cycles 2 and 3 • Course of gonadotropins (FSH, LH) • Endometrial growth • Pharmacokinetics of E1, E2, and DRSP in treatment cycle 3
Evaluation Criteria:	Efficacy (Primary): • The proportion of subjects with ovulation in at least one of the treatment cycles 2 and 3, based on the binary variable "ovulation" (i.e., Hoogland score 6) with the levels "yes" and "no". Efficacy (Secondary): • Hoogland score, categorical variable with the levels "no activity", "potential activity","non-active follicle-like structure", "active Follicle-like structure (FLS)", "luteinized unruptured follicle", and "ovulation" • Laboratory values for progesterone, FSH, and LH, • Endometrial thickness, • Follicle size.

	Safety: • Adverse events, physical and gynecological examinations, electrocardiogram (ECG), TVU, and standard safety laboratory analyses in blood and urine. • Hormones/proteins in serum: Thyroid-stimulating hormone (TSH), prolactin, total/free testosterone, androstenedione, dehydroepiandrosterone-sulfate (DHEA-S), cortisol, sex hormone-binding globulin (SHBG), corticoid-binding globulin (CBG), thyroxine-binding globulin (TBG). • Body weight; blood pressure; heart rate; bleeding pattern (daily recording of bleeding intensity by using a diary); additional TVU parameters/findings, e.g., ovarian cysts (pre-treatment and treatment cycles, follow-up).
	Pharmacokinetics: Blood samples were collected in both treatment groups in cycle 3 in order to estimate the exposure to DRSP, E2, and E1 by a population pharmacokinetic approach using nonlinear mixed effects model. Pharmacokinetic data was evaluated as follows: • Definition of a suitable structural pharmacokinetic model to characterize the pharmacokinetics of DRSP and E2 in the two treatment groups. • Estimation of the population pharmacokinetic parameters and their associated precision and variability. • Estimation of inter-individual 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 pharmacokinetic behavior of DRSP and E2.
Statistical Methods:	Efficacy (Primary): 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 two treatments. Efficacy (Secondary): The time course of the serum levels of progesterone, LH, FSH, and follicle sizes was summarized using descriptive statistics. Change in the endometrial thickness was analyzed using descriptive statistics. Safety: Descriptive statistics were used.
	Pharmacokinetics: Population pharmacokinetic parameters were summarized using descriptive statistics.

Number of Subjects:	Planned: 50 (up to 58 subjects per arm, up to 116 subjects total) Analyzed: 52/51 Safety Set (SS); 49/48 Full Analysis Set (FAS); 44/45 Per-Protocol Set (PPS).

Study Results

Results Summary — Subject Disposition and Baseline

The study population consisted of healthy young women with proven ovulation during the pre-treatment cycle, the target group for contraceptive medication.

One-hundred-and-five out of 192 screened subjects were randomized. One-hundred-and-three of them started treatment and thus comprised the safety analysis set. Eleven subjects discontinued at some point after the first intake of study drug, and 92 subjects completed the study period of 84 days as scheduled.

Ninety-seven subjects were included in the FAS, as they had remained in the study for 2 complete treatment cycles. Eight subjects from the FAS were excluded from the PPS (n = 89) as they did not complete the third treatment cycle (n=6) or because of major protocol violations (n =2).

The proportions of withdrawals and finishers were always similar for both treatment regimens. The subjects in the safety analysis set had a mean age of 28.4 years (median age: 28.0 years, range: 18 - 35) and a mean body mass index (BMI) of 21.4 kg/m^2 (range: 18 - 26 kg/m^2). With the exception of one Asian in each treatment group, all other subjects were Caucasians.

Results Summary — Efficacy

The primary efficacy parameter was the proportion of subjects with an ovulation in treatment cycle 2 or 3. For each regimen, 1 case of ovulation was recorded, resulting in ovulation rates of 2.3% (PPS population, mono DRSP 1x treatment) and 2.2% (tri dec DRSP treatment). The 90% confidence interval ranged from 0.1% to 10.3% and from 0.1% to10.1%, respectively.

Regarding secondary efficacy parameters, there were no relevant differences of the results between FAS and PPS.

Ovarian activity, expressed by means of the Hoogland score, is listed in Table 1.

Table 1: Ovarian activity by treatment (Hoogland Score) - FAS

Full Analysis Set	Ovarian activity, grading	mono DRSP 1x	tri dec DRSP
Treatment cycle 2	**No. of volunteers**	**49 (100%)**	**48 (100 %)**
	Missing	0 (0.0%)	0 (0.0%)
	No activity (Hoogland 1)	21 (42.9%)	16 (33.3%)
	Potential activity (Hoogland 2)	11 (22.4%)	11 (22.9%)
	Active FLS (Hoogland 4)	17 (34.7%)	20 (41.7%)
	Ovulation (Hoogland 6)	0 (0.0%)	1 (2.1%)
	Not assessable	0 (0.0%)	0 (0.0%)
Treatment cycle 3	**No. of volunteers**	**45 (100%)**	**47 (100%)**
	Missing	0 (0.0%)	1 (2.1%)
	No activity (Hoogland 1)	21 (46.7%)	19 (40.4%)
	Potential activity (Hoogland 2)	7 (15.6%)	11 (23.4%)
	Active FLS (Hoogland 4)	15 (33.3%)	16 (34.0%)
	Ovulation (Hoogland 6)	1 (2.2%)	0 (0.0%)
	Not assessable	1 (2.2%)	0 (0.0%)

A complete suppression of ovarian activity (i.e., Hoogland 1) was observed in less than 50% of the subjects. Approximately 1/3 of the subjects had follicles larger than 13 mm (Hoogland 4).

Mean FSH and LH values during the treatment cycles were lower as compared to the pre-treatment cycle, especially at mid-cycle where a peak value is to be expected.

Mean serum progesterone was continuously suppressed to approximately 1 to 2 nmol/L from the first sampling point in cycle 1 onwards (day 6) in both groups. Especially at the end of the cycle mean values were clearly lower as compared to the pre-treatment cycle. A maximum progesterone value of 12.2 nmol/L and 36 nmol/L was measured in one subject of the mono DRSP 1x group for treatment cycle 3 and in one subject of the tri dec DRSP group for treatment cycle 2, respectively. In accordance with their transvaginal ultrasound findings, ovulation occurred in these two subjects.

The normal pattern of endometrial growth that had been observed in the pre-treatment cycle was also suppressed from the first treatment cycle onwards in both groups. Endometrial thickness remained at the same level of approximately 3 - 5 mm in each cycle.

Although mean values for maximum follicle size at each day were not obviously different from the pre-treatment cycle due to high variation, the distribution of maximum follicle size categories was shifted towards smaller diameters in both treatment groups. In accordance with the Hoogland categorization, in cycles 2 and 3, 50 to 65% of the subjects only had follicles measuring <13 mm. However, follicles >20 mm were detected in approximately 20% and follicles >30 mm in 3 - 4% of the women. In addition, the timing of follicle growth

changed under treatment. While maximum follicle sizes were reached on cycle day 12 in the pre-treatment cycles by most subjects mono DRSP 1x group, 65.3%, and tri dec DRSP group, 56.3%), no mid-cycle cluster of maximum follicle size days was observed under treatment in both groups. Often, the maximum follicle size was already observed at the beginning of the treatment cycle.

Results Summary — Safety

No deaths were reported during this study. One non-fatal serious adverse event (SAE) occurred in the follow-up period of the study (One subject was hospitalized for pneumonia; adverse event not-related to study drug). Two subjects prematurely discontinued their study medication due to an adverse event: one subject experienced painful swelling, paraesthesia and decreased mobility of all four extremities (possibly rheumatoid arthritis, adverse event not related to study drug); another subject had an abnormal cervical smear (adverse event related to study drug).

The most frequently reported adverse events were nasopharyngitis (37.9%), albuminuria (34.0 %), and headaches (31.1%). The most frequent adverse event with a possible causal relation to study drug intake were headaches, decreased and increased body weight, and acne. Abdominal pain was more frequent under tri dec DRSP treatment than under mono 1x DRSP (21.6% vs 5.8%, respectively). The same applied for nausea (11.8% vs 3.8%, respectively), weight gain (17.6 vs 9.6%, respectively), and increased bilirubin values (13.7% vs 5.8%, respectively). Acne and headaches were more frequent with mono DRSP. Most events were mild or moderate in severity.

With the exception a decrease of about 30% in serum ferritin values in both groups, no clinically relevant time- or group-related trends were detected for any of the assessed laboratory parameters. Increases in hormone-binding proteins (TBG, CBG, SHBG) were observed in treatment cycle 3 as compared to the pre-treatment cycle. Androgen levels (androstenedione, testosterone) were decreased after administration of both E2/DRSP regimens.

Other safety evaluations comprised vital signs and gynecological examinations as well as an analysis of bleeding patterns and cycle control. No time- or group-related trends were detected for blood pressure and pulse rate. One subject in each treatment group progressed from Pap 2 at screening to Pap 3 at the follow-up examination. In two additional subjects, a necessary repetition of the cervical smear due to ambiguous results showed a Pap 3 finding. The mean number of bleeding/spotting days was slightly lower in the tri dec DRSP group as compared to the mono DRSP 1x group. The number of subjects documenting a withdrawal bleeding was higher for the triphasic treatment in the first and third treatment cycles as compared to the monophasic regimen. Less subjects reported an intracyclic bleeding in the mono DRSP treatment group.

Results Summary — Pharmacokinetics

The evaluation of the pharmacokinetic data for drospirenone, estradiol and estrone during the third treatment cycle will be contained in a separate report.

Conclusion(s)
In this study, the administration of two different E2/DRSP regimens for 3 treatment cycles was well tolerated. The only SAE (pneumonia) occurred in the follow-up phase. The frequency and type of adverse events do not differ from those expected after administration of these two hormones. In both treatment regimens, an ovulation was detected in one subject (approximately 2% of the subjects). Approximately 30% of the subjects in both groups showed large follicles during treatment. Pharmacokinetic results will be described in a separate report.

Publication(s):	None		
Date Created or Date Last Updated:	19 APR 2012	Date of Clinical Study Report:	17 DEC 2009

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen, Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Bayer Pharma AG	Global Drug Discovery Clinical Pharmacology Sellerstr. 31	13353	Berlin	GERMANY
2	Dinox GmbH Berlin	Anklamer Str. 38	10115	Berlin	GERMANY