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:	91765 (311926)	NCT00653614
Study Phase:	II	
Official Study Title:	A multi-center, double-blind, randomized, parallel-group study to evaluate cycle control and safety of 6 different regimens of an oral contraceptive containing estradiol and drospirenone in healthy female subjects aged between 18 and 35 years over 7 cycles	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	E2/DRSP (BAY 86-4891, GA)	
Name of Active Ingredient:	17-β Estradiol (E2; ZK 5018) and Drospirenone (DRSP; ZK 30595)	
Dose and Mode of Administration:	Subjects were assigned to one of the 6 study formulations containing E2/DRSP in different dosing regimens (Table 1), during a treatment cycle.	
Reference Therapy/Placebo		
Reference Therapy:	None	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	7 treatment cycles; each cycle consisting of 28 days (total 196 days), one tablet per day.	
Studied period:	Date of first subjects' first visit:	12 MAR 2008
	Date of last subjects' last visit:	09 JUN 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	The study was conducted according to the final protocol version from February 21, 2008, and included no substantial amendments.	
Study Centre(s):	This study was conducted in 27 centers in Germany.	

Table 1: Six different treatment regimens of E2/DRSP

	Mono DRSP 1x	Mono DRSP 2x	Tri con DRSP	Tri con DRSP 1x	Tri dec DRSP	Tri dec DRSP 1x
Days 1–8	E2/1.5mg DRSP/3 mg	E2/1.5mg DRSP/3 mg	E2/1 mg DRSP/3 mg	E2/1 mg DRSP/3 mg	E2/1 mg DRSP/3 mg	E2/1 mg DRSP/3 mg
Days 9 – 16	E2/1.5mg DRSP/3 mg	E2/1.5mg DRSP/3 mg	E2/1.5 mg DRSP/3 mg	E2/1.5 mg DRSP/3 mg	E2/1.5 mg DRSP/2.5 mg	E2/1.5 mg DRSP/2.5 mg
Days 17 – 24	E2/1.5mg DRSP/3 mg	E2/1.5mg DRSP/3 mg	E2/2 mg DRSP/3 mg	E2/2 mg DRSP/3 mg	E2/2 mg DRSP/2 mg	E2/2 mg DRSP/2 mg
Day 25	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Day 26	Placebo	DRSP/3 mg	Placebo	Placebo	Placebo	Placebo
Day 27	DRSP/3 mg	Placebo	Placebo	DRSP/3 mg	Placebo	DRSP/2 mg
Day 28	Placebo	DRSP/3 mg	Placebo	Placebo	Placebo	Placebo

All the doses in the 6 different treatment regimens were administered orally.

Methodology:	This multicenter, double-blind, randomized, parallel group study consisted of Visit 1 (Screening visit), Visit 2 (admission to treatment), Visit 3 (around cycle 4, i.e., treatment days 106 - 112) and Visit 4 (Final examination, i.e., 14 days after end of treatment). Each treatment was initiated after a screening period (maximum of 6 weeks) and was administered daily for 7 cycles of 28 days each without a pill-free interval, i.e., for 196 consecutive days. The tablet intake started on the first day of the first menstrual/withdrawal bleeding after Visit 2, regardless of whether the subject was a first-time user (starter) or was switching from another combined oral contraceptive (COC) (switcher). In the following cycles, tablet intake was not triggered by any bleeding events. The focus of the investigation was the bleeding pattern associated with the 6 treatment schemes. Tablet intake and bleeding events were documented by the subjects on a daily basis on the diary cards provided. A urine pregnancy ß-human chorionic gonadotropin (ß-HCG) test was performed at the investigator's site at Visit 2 and Visit 4. The acceptance of study treatment was also assesed by taking subjective assessment of the subjects' overall satisfaction with the study oral contraceptives (OC).
Indication/ Main Inclusion Criteria:	Indication: Hormonal contraception Main Inclusion Criteria: • Healthy female subjects, aged 18 to 35 years, inclusive • History of regular cyclic menstrual periods (with a cycle length between 25 and 35 days) • Willingness to use barrier methods of contraception (condoms with spermicide, diaphragms with spermicide, spermicidal vaginal suppositories) or abstinence during the trial
Study Objectives:	Overall: To evaluate and compare the cycle control, bleeding patterns, and safety of six different treatment regimens with E2/DRSP during administration for 7 treatment cycles.
Evaluation Criteria:	Efficacy (Primary): • Number of intracyclic bleeding episodes (including spotting) in Cycles 2 to 7. Efficacy (Secondary): • Assessment of bleeding patterns and cycle control Safety: • Baseline findings and adverse events (AE) • Safety laboratory tests (including pregnancy tests) • Vital signs • Physical and gynecological examination (including breast palpation, transvaginal ultrasonography [TVU] and cytological cervical smear) • Comparison of safety of the different treatment regimens

Statistical Methods:	Efficacy (Primary): A proportional odds model was applied to fit the primary variable and to compare the treatment with the lowest mean number μ_0 of intracyclic bleeding episodes (including spotting) with the other 5 treatment regimens. The acceptance of treatment was analyzed descriptively using the number and percentage of the observations in each category. Efficacy (Secondary): The secondary variables were also analyzed applying the proportional odds model. An acceptable treatment regimen with regard to bleeding behavior was selected based on the results of the proportional odds model for the intracyclic bleeding episodes, intracyclic bleeding days, withdrawal bleeding episodes, and the results of other cycle control indices. Safety: For analysis, AEs were coded using the MedDRA dictionary, version 12.0.
Number of Subjects:	A total of 6 x 100 subjects were planned, 670 subjects were initially screened, 635 randomised and 628 subjects were finally enrolled and analyzed groupwise: Mono DRSP 2x: 107 Mono DRSP 1x: 108 Tri dec DRSP: 105 Tri con DRSP: 103 Tri con DRSP 1x: 103 Tri dec DRSP 1x: 102

Study Results

Results Summary — Subject Disposition and Baseline

A screening of 670 healthy female subjects, aged 18 to 35 years inclusive, resulted in the classification of 35 subjects (5.2%) as screening failures [listing-only set (LOS)] and 635 subjects (94.8%) as eligible for the study. Of all 635 subjects randomized to the treatment, there were 7 subjects who either did not receive the study medication or did not provide any data after the start of the treatment phase (LOS). As a result, 628 subjects (93.7% of the screened population) received the study medication and provided the study data for analysis [full analysis set (FAS) = 628 (100.0%)]. Of them, 574 subjects (91.4%) completed and 54 (8.6%) prematurely discontinued the study treatment. The per-protocol set (PPS) consisted of 529 subjects (79.9% of the screened population). All evaluations are based on analysis of the FAS of 628 subjects (100.0%), if not otherwise specified.

The mean age of the subject sample was 24.8 ± 4.36 years (values ranged between 18 and 36 years with a median of 24.0 years). At least 75% of the subjects were of 28 years age and younger. Nearly all subjects were of Caucasian origin, with 4 exceptions (3 Asians and 1 Mulatto). Mean body mass index (BMI) was 22.78 ± 2.952 kg/m^2 (values ranged between 16.0 and 29.9 kg/m^2). The majority of subjects, 590 (93.9%), reported to be sexually active; only 38 subjects (6.1%) denied this question. Slightly more than 1/3 of the subjects, 217 (34.6%), reported to smoke (average number of cigarettes ranging between 1 and 20, median of 8.0); 411 subjects (65.4%) reported to be non-smokers. A high number of

subjects, 451 (71.8%), reported seldom alcohol consumption, followed by 119 subjects (18.9%) with occasional alcohol consumption, and 58 subjects (9.2%) stated that they never consumed alcohol. In general, the treatment groups were well matched in terms of basic characteristics.

Results Summary — Efficacy

The primary aim of this study was to investigate the bleeding characteristics of the six E2/DRSP regimens and to rank the regimens in view of the primary variable. The primary variable to evaluate cycle control was the number of intracyclic bleeding episodes (including spotting) during Cycles 2 to 7. The statistical testing of the regimens in terms of the number of intracyclic bleeding episodes (including spotting) during Cycles 2 to 7 revealed that, within the FAS, Tri con DRSP and Tri dec DRSP1x were less favorable than Tri con DRSP1x (p=0.032 and 0.0146). The relative magnitudes of the estimates implied the preference order of the regimens (mean of intracyclic bleeding episodes/estimate):

- Tri con DRSP1x (1.06/0)
- Mono DRSP2x (1.21/-0.17)
- Mono DRSP1x (1.22/-0.28)
- Tri dec DRSP (1.38/-0.35)
- Tri con DRSP (1.45/-0.56)
- Tri dec DRSP1x (1.96/-0.64)

The comparative analysis of the regimens in terms of the number of intracyclic bleeding days (including spotting) during Cycles 2 to 7 (secondary variable), within the FAS concluded that the Tri dec DRSP1x was less favorable than Tri con DRSP1x (p=0.0031) and the following preference order of the regimens (mean of intracyclic bleeding days/estimate) was established:

- Tri con DRSP1x (4.13/0)
- Mono DRSP2x (5.99/-0.30)
- Mono DRSP1x (6.24/-0.36)
- Tri con DRSP (6.45/-0.57)
- Tri dec DRSP (7.33/-0.48)
- Tri dec DRSP1x (9.42/-0.78)

With regard to the number of withdrawal bleeding episodes in Cycles 1 to 6 (secondary variable), the 3 treatments Tri con DRSP1x, Mono DRSP1x, and Mono DRSP2x showed less withdrawal bleeding episodes than Tri con DRSP ($p<0.05$). The following preference order of the regimens (mean of withdrawal bleeding episodes/estimate) was established:

- Tri con DRSP (5.11/0)
- Tri dec DRSP (5.00/-0.11)
- Tri dec DRSP1x (4.83/0.29)
- Tri con DRSP1x (4.20/0.86)
- Mono DRSP1x (3.95/1.15)
- Mono DRSP2x (3.63/1.38)

Based on the results of the ranking analysis, it can be concluded that the regimens with constant DRSP dose of 3 mg on Days 1 to 24 and the addition of 3 mg DRSP on individual days (1 or 2) within the interval of Days 26 to 28 were associated with less intracyclic bleeding; concurrently, the same regimens were connected with a significant decrease of the withdrawal bleeding episodes.

All other bleeding parameters were exploratively analyzed over the treatment period. An overview of the most and least preferable regimens as concluded from the frequency of subjects with at least 1 intracyclic bleeding during Cycles 2 to 6 and 2 to 7 is shown in Table 2.

Table 2: Explorative overall analysis focused on most/least preferable treatment regimen regarding subjects with at least one intracyclic bleeding episode

Bleeding parameters		**Regimens**	
Cycle control		**Most preferable**	**Least preferable**
Number of volunteers with intracyclic bleeding (including spotting)			
	At least 1 episode in **Cycles 2 – 6**	Tri ***con*** DRSP1x	Tri ***con*** DRSP
	At least 1 episode in **Cycles 2 – 7**	Tri ***con*** DRSP1x	Tri ***con*** DRSP
Number of volunteers with intracyclic bleeding (excluding spotting)			
	At least 1 episode in **Cycles 2 – 6**	Tri ***con*** DRSP1x	Tri **dec** DRSP1x
	At least 1 episode in **Cycles 2 – 7**	Tri ***con*** DRSP1x	Tri **dec** DRSP1x

An overview of the most and least preferable regimens as exploratively analyzed focusing on the second half of the treatment period is displayed in Table 3 and Table 4. The reason for this approach was that the initially disturbed bleeding pattern after the beginning of a new OC (if any) usually stabilizes after the first 2-3 treatment cycles.

Table 3: Explorative analysis of selected bleeding parameters focused on most/least preferable treatment regimen during the second half of the treatment period (90-day reference period method)

Bleeding parameters		**Regimens**	
Bleeding pattern		**Most preferable**	**Least preferable**
90-day reference **Period 2**	Number of bleeding/spotting days	Mono DRSP2x	Tri **dec** DRSP1x
	Number of bleeding days (excluding spotting)	Mono DRSP2x	Tri **dec** DRSP
	Number of spotting-only days	Tri ***con*** DRSP1x	Tri **dec** DRSP1x
	Number of bleeding/spotting episodes	Mono DRSP2x	Tri **dec** DRSP1x
	Mean length of bleeding/spotting episodes	Tri ***con*** DRSP	Mono DRSP1x
	Maximum length of bleeding/spotting episodes	Tri ***con*** DRSP	Mono DRSP1x
	Range of length of bleeding/spotting episodes	Tri ***con*** DRSP1x	Tri **dec** DRSP1x

Table 4: Explorative analysis of selected bleeding parameters focused on most/least preferable treatment regimen during the second half of the treatment period (by-cycle analysis)

Bleeding parameters			Regimens	
Cycle control			Most preferable	Least preferable
Withdrawal bleeding	Number of volunteers with *withdrawal* bleeding	Cycle 4	Tri ***con*** DRSP	*Mono* DRSP2x
		Cycle 5	Tri **dec** DRSP	*Mono* DRSP2x
		Cycle 6	Tri **dec** DRSP	*Mono* DRSP2x
	Mean length of *withdrawal* bleeding episodes	Cycle 4	Tri ***con*** DRSP	*Mono* DRSP2x
		Cycle 5	Tri ***con*** DRSP	Tri **dec** DRSP1x
		Cycle 6	Tri ***con*** DRSP	Tri **dec** DRSP1x
	Maximum intensity of *withdrawal* bleeding episodes	Cycle 4	*Mono* DRSP2x	Tri **dec** DRSP
		Cycle 5	*Mono* DRSP2x	Tri **dec** DRSP, Tri **dec** DRSP1x
		Cycle 6	*Mono* DRSP2x	Tri **dec** DRSP
	Onset of *withdrawal* bleeding episodes	Cycle 4	Tri **dec** DRSP1x	*Mono* DRSP2x
		Cycle 5	Tri ***con*** DRSP1x	*Mono* DRSP2x
		Cycle 6	Tri ***con*** DRSP	*Mono* DRSP1x
Intracyclic bleeding (including spotting)	Number of volunteers with *intracyclic* bleeding	Cycle 4	Tri ***con*** DRSP1x	Tri **dec** DRSP
		Cycle 5	Tri ***con*** DRSP1x	Tri **dec** DRSP1x
		Cycle 6	*Mono* DRSP1x	Tri **dec** DRSP1x
	Number of *intracyclic* bleeding episodes	Cycle 4	*Mono* DRSP2x, Tri ***con*** DRSP1x	Tri **dec** DRSP1x
		Cycle 5	Tri ***con*** DRSP1x	Tri **dec** DRSP1x
		Cycle 6	*Mono* DRSP1x, Tri ***con*** DRSP	Tri **dec** DRSP1x
	Maximum length of *intracyclic* bleeding episodes	Cycle 4	Tri ***con*** DRSP1x	*Mono* DRSP1x
		Cycle 5	Tri ***con*** DRSP1x	Tri **dec** DRSP
		Cycle 6	Tri **dec** DRSP	*Mono* DRSP1x
	Number of *intracyclic* bleeding days	Cycle 4	Tri ***con*** DRSP1x	*Mono* DRSP1x
		Cycle 5	Tri ***con*** DRSP1x	Tri **dec** DRSP1x
		Cycle 6	Tri ***con*** DRSP	Tri **dec** DRSP1x
	Maximum intensity of *intracyclic* bleeding episodes	Cycle 4	Tri ***con*** DRSP1x	Tri ***con*** DRSP
		Cycle 5	Tri ***con*** DRSP1x, Tri ***con*** DRSP	Tri **dec** DRSP
		Cycle 6	Tri **dec** DRSP	*Mono* DRSP2x

Results Summary — Safety

Adverse events:

A total of 206 of 628 subjects (32.8%) reported at least 1 AE during the study. The highest number of subjects with AEs, 44 (42.7%), was seen with the regimen Tri con DRSP1x; the lowest number of subjects with AEs, 28 (26.7%), was seen with the regimen Tri dec DRSP. The frequency of subjects with AEs with the remaining 4 treatment regimens ranged between 30 (29.1%) and 37 (34.3%).

No deaths were reported. A total of 15 AEs (of all 349 AEs) in 13 subjects (2.1%) were rated as serious AEs. The SAEs were distributed among all treatment groups except for Tri dec

DRSP1x. The following SAEs occurred within the frame of this study: Cervix carcinoma stage 0 (3 cases), Circulatory collapse and Concussion (1 case), Blast injury (1 case), Gastroenteritis (1 case), Hodgkin's disease (1 case), Appendicitis (1 case), Ligament rupture (1 case), Abortion induced (1 case), Imminent abortion (1 case), Constipation (1 case), Accident and Lower limb fracture (1 case). The study drug was withdrawn in 1 case only, namely in the case of Hodgkin's disease. For all other SAEs, the most relevant study drug actions were "dose not changed" in 7 cases and "not applicable" (when the AE had occurred after end of study treatment) in 5 cases. None of the SAEs was considered as drug-related. All SAEs recovered/resolved with exception of 2, namely Cervix carcinoma stage 0 (in 1 subject; follow-up information missing at the time of report writing) and Hodgkin's disease.

The study drug was withdrawn due to AE in 29 cases (4.6%). A total of 32 AEs (of all 349 AEs) leading to drug withdrawal were recorded; there were 3 subjects who reported 2 AEs each as a reason for premature treatment discontinuation. The number of subjects discontinued due to AE varied between 2 (1.9%) with the regimen Tri con DRSP and 7 (6.8% and 6.9%) with the regimens Tri con DRSP1x and Tri dec DRSP1x, respectively. The majority of AEs that resulted in drug withdrawal pertained to the system organ class (SOC) Reproductive system and breast disorders, as follows: Vaginal haemorrhage (6 cases), Metrorrhagia (2 cases), Menorrhagia (2 cases), Hypomenorrhoea, Dysmenorrhoea, and Vaginal discharge. In addition, at the further positions were the SOC Gastrointestinal disorders: Nausea (2 cases) and Constipation (2 cases); the SOC Investigations: Weight increased (4 cases); the SOC Nervous system disorders: Headache (2 cases), Migraine, and Dizziness; and the SOC Skin and subcutaneous tissue disorders: Acne (2 cases) and Seborrhoea. The following SOCs were represented with single AEs leading to drug withdrawal: SOC Infections and infestations (Tonsillitis); SOC Neoplasms benign, malignant and unspecified (Hodgkin's disease); SOC Psychiatric disorders (Depression); and SOC Vascular disorders (Essential hypertension). The following AEs led most frequently to premature drug discontinuation: Vaginal haemorrhage in 6 subjects (1.0%) and Weight increased in 4 subjects (0.6%); further AEs leading to premature drug withdrawal in >1 subject were Metrorrhagia, Menorrhagia, Constipation, Nausea, Headache, and Acne in 2 subjects each (0.3%). The outcome of most of the AEs leading to drug withdrawal was recovered/resolved. Not recovered/not resolved at the time of database closure were the following AEs: Weight increased (3 cases), Hodgkin's disease, and Metrorrhagia (1 case). The AEs Acne (1 case) and Essential hypertension were recovering/resolving at the end of the study. The outcome of the following 3 AEs remained unknown: Acne and Seborrhoea (in 1 subject) and Constipation (1 case). In terms of drug relationship, 27 of all 32 AEs leading to drug withdrawal were considered as drug-related. The 5 unrelated AEs were Constipation (2 cases), Hodgkin's disease, Tonsillitis, and Dizziness.

The total number of AEs amounted to 349. The highest number of 73 AEs was seen with the regimen Tri con DRSP1x affecting 44 subjects (42.7%); the lowest numbers of AEs were seen with the regimens Tri dec DRSP, i.e., 45 AEs in 28 subjects (26.7%) and Tri dec DRSP1x, i.e., 45 AEs in 31 subjects (30.4%). The most frequent AEs (in >1% of the total sample) were as follows (by preferred term, MedDRA Version 12.0): Nasopharyngitis in 28 subjects (4.5%), Headache in 20 subjects (3.2%), Acne and Cystitis in 18 subjects (2.9%) each, Diarrhoea in 13 subjects (2.1%), Cervical dysplasia in 10 subjects (1.6%), Vaginal infection and Vulvovaginal candidiasis in 9 subjects (1.4%) each, Dysmenorrhoea in 8 subjects (1.3%), and Bronchitis, Vomiting, and Weight increased in 7 subjects (1.1%) each. Alopecia, Skin disorder, and Vaginal haemorrhage occurred in 6 subjects (1.0%) each.

The most frequently affected MedDRA SOCs in the total sample were as follows: Infections and infestations [126 AEs in 94 subjects (15.0%)], Reproductive system disorders [48 AEs in 43 subjects (6.8%)], Gastrointestinal disorders [47 AEs in 39 subjects (6.2%)], Skin and subcutaneous tissue disorders [34 AEs in 29 subjects (4.6%)], Nervous system disorders [28 AEs in 23 subjects (3.7%)], Investigations [16 AEs in 16 subjects (2.5%)], Injury, poisoning

and procedural complications [10 AEs in 8 subjects (1.3%)], and Musculoskeletal and connective tissue disorders [8 AEs in 7 subjects (1.1%)]; the AEs classified to other SOCs affected less than 1% of the subjects in the study.

The relationship to the study drug for the individual AEs was assessed as follows: AEs in 56 subjects (8.9%) were assessed as related and AEs in 150 subjects (23.9%) as non-related to the study drug. The AEs of the following SOCs (ordered by frequency of subjects with AEs) were rated as related to the study drug: 1) Skin and subcutaneous tissue disorders in 20 subjects (3.2%) [AEs: Acne in 13 subjects (2.1%), Alopecia in 1 subject (0.2%), Neurodermatitis in 1 subject (0.2%), Seborrhoea in 1 subject (0.2%), and Skin disorder in 6 subjects (1.0%)], 2) Reproductive system and breast disorders in 18 subjects (2.9%) [Breast pain in 1 subject (0.2%), Dysmenorrhoea in 3 subjects (0.5%), Endometrial hypertrophy in 1 subject (0.2%), Hypomenorrhoea in 1 subject (0.2%), Menorrhagia in 2 subjects (0.3%), Metrorrhagia in 2 subjects (0.3%), Pelvic pain in 1 subject (0.2%), vaginal discharge in 1 subject (0.2%), and Vaginal haemorrhage in 6 subjects (1.0%)], 3) Nervous system disorders in 11 subjects (1.8%) [AEs: Headache in 10 subjects (1.6%) and Migraine in 1 subject (0.2%)], 4) Investigations in 6 subjects (1.0%) [AE: Weight increased in 6 subjects (1.0%)], 5) Psychiatric disorders in 5 subjects (0.8%) [AEs: Affect lability in 1 subject (0.2%), Depression in 2 subjects (0.3%), Libido decreased in 1 subject (0.2%), and Mood swings in 1 subject (0.2%)], 6) Gastrointestinal disorders in 3 subjects (0.5%) [AE: Nausea in 3 subjects (0.5%)], 7) Vascular disorders in 2 subjects (0.3%) [AEs: Essential hypertension in 1 subject (0.2%) and Hot flush in 1 subject (0.2%)], and 8) Musculoskeletal and connective tissue disorders in 1 subject (0.2%) [AE: Pubic pain in 1 subject (0.2%)]. More frequent drug-related AEs (in ≥3 subjects) were: Acne in 13 subjects (2.1%), Headache in 10 subjects (1.6%), Skin disorder in 6 subjects (1.0%), Vaginal haemorrhage in 6 subjects (1.0%), Weight increased in 6 subjects (1.0%), and Dysmenorrhoea in 3 subjects (0.5%). There were no AEs with a relationship to the study conduct or any study procedures.

The maximal intensity of AEs was mild in 79 subjects (12.6%), moderate in 108 subjects (17.2%), and severe in 11 subjects (1.8%) in the total sample. The outcome of AEs was "recovered/resolved" for 310 AEs in 185 subjects (29.5%); "recovering/resolving" were 12 AEs in 12 subjects (1.9%) and "not recovered/not resolved" at the time of database closure remained 22 AEs in 21 subjects (3.3%).

Common AEs (as specified in the Investigator's Brochure) were reported most frequently for:

- SOC Nervous system [Headache - 24 AEs in 20 subjects (3.2%)]
- SOC Skin and subcutaneous tissue disorders [Acne - 18 AEs in 18 subjects (2.9%)]
- SOC Reproductive system disorders [Breast pain - 4 AEs in 4 subjects (0.6%); Breast enlargement was not reported; Dysmenorrhoea - 11 AEs in 8 subjects (1.3%); Metrorrhagia - 2 AEs in 2 subjects (0.3%)]
- SOC Gastrointestinal disorders [Abdominal pain - 2 AEs in 2 subjects (0.3%); Abdominal pain lower - 3 AEs in 3 subjects (0.5%); Abdominal pain upper - 1 AE in 1 subject (0.2%)]
- SOC Investigations [Weight increased 7 AEs in 7 subjects (1.1%)]
- SOC Psychiatric disorders [Emotional lability - 1 AE in 1 subject (0.2%)].

Most frequent common AEs were as follows: Headache - 24 AEs in 20 subjects (3.2%), Acne - 18 AEs in 18 subjects (2.9%), Dysmenorrhoea - 11 AEs in 8 subjects (1.3%), Weight increased - 7 AEs in 7 subjects (1.1%), Breast pain - 4 AEs in 4 subjects (0.6%), Abdominal pain lower - 3 AEs in 3 subjects (0.5%), Abdominal pain - 2 AEs in 2 subjects (0.3%), and Metrorrhagia - 2 AEs in 2 subjects (0.3%). The following AEs occurred in single subjects (0.2%): Abdominal pain upper and Emotional lability. The number of AEs comprised of the expected AEs reported during the study independently from the rating of the relationship by the investigator, i.e., including both related and non-related AEs.

Safety laboratory tests displayed normal and stable results. Increased leukocyte counts reaching the alert range in 3 subjects (0.5%) at Final examination were associated with ongoing AEs (Crohn's disease, Vaginal infection as a result of abrasion following Imminent abortion, and Nasopharyngitis). Decreased leukocyte counts (in 5 cases), platelet counts (in 2 cases), and potassium and alanine transaminase (ALAT) values (in 1 case each) were of transient nature; repeated tests yielded normal results.

Seven pregnancies were registered during the frame of the study (condoms were mandatory because of still missing proof of the contraceptive efficacy of the regimens): 2 before start, 3 after end of the treatment, and 2 during the treatment. The pregnancies that occurred during the study treatment were associated with diarrhea in both the cases plus ruptured condom in one of the cases.

Conclusion(s)

In this study, the aim to facilitate the selection of the most suitable regimen for Phase-3 development based on the cycle control parameters resulted in statistical proof of the preference of the regimen Tri con DRSP1x as compared to the Tri con DRSP and Tri dec DRSP1x in terms of the number of intracyclic bleeding episodes (including spotting) during Cycles 2 to 7. The same regimen, Tri con DRSP1x, proved to be preferable to Tri dec DRSP1x also in terms of the number of intracyclic bleeding days (including spotting) during Cycles 2 to 7. However, this regimen was associated with significantly decreased occurrence of withdrawal bleeding episodes as compared with the regimens Tri con DRSP, Tri dec DRSP, and Tri dec DRSP1x.

The exposure of 628 subjects to E2/DRSP for 7 treatment cycles was well tolerated and the general safety profile of the 6 different dosing regimens gave no reasons for concern. No unfavorable changes in the parameters of clinical relevance were documented.

Publication(s):	None		
Date Created or Date Last Updated:	04 JUN 2012	Date of Clinical Study Report:	11 NOV 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	Frauenarztpraxis Dipl. med. Michael Stellmacher	J.-S.-Bach Str. 56	39288	Burg	GERMANY
2	Frauenarztpraxis Dr. Bernd Pittner	Facharzt für Frauenheilkunde Pfaffensteinstrasse 8	04207	Leipzig	GERMANY
3	Frauenarztpraxis Dr. med. Wolfram Brach	Am Stadtbrunnen 8 - 10	63128	Dietzenbach	GERMANY
4	Frauenarztpraxis Dr. Robert Hantschel	An der Niedermühle 8	01744	Dippoldiswalde	GERMANY
5	Frauenarztpraxis Dr. Wetzel	Helsunger Str. 7	38889	Blankenburg	GERMANY
6	Frauenarztpraxis Hr. Dr. H. Lindecke	Frankfurter Allee 54	10247	Berlin	GERMANY
7	Kreiskrankenhaus Krumbach	Mindelheimerstr. 69	86381	Krumbach	GERMANY

8	Kreiskrankenhaus Krumbach	Mindelheimerstr. 69	86381	Krumbach	GERMANY
9	Praxis Dr. Larbig	Frauenarztpraxis Bahnhofstrasse 26	36037	Fulda	GERMANY
10	Praxis Fr. C. Burgkhardt	Frauenarztpraxis Gletschersteinstrasse 34	04299	Leipzig	GERMANY
11	Praxis Fr. Dr. A. Braune	Frauenarztpraxis Domplatz 11	39104	Magdeburg	GERMANY
12	Praxis Fr. Dr. B. Heuberger	Frauenarztpraxis Lindenallee 16	12587	Berlin	GERMANY
13	Praxis Fr. Dr. G. Gollnick	Frauenarztpraxis Waldschloesschenstr. 3A	01099	Dresden	GERMANY
14	Praxis Fr. Dr. J. Tyagi	Mozartstr. 2	63165	Mühlheim	GERMANY
15	Praxis Fr. Dr. K. Maar	Frauenarztpraxis Alt-Tegel 13	13507	Berlin	GERMANY
16	Praxis Fr. I. Gröger	Schillerstr. 44	04808	Wurzen	GERMANY
17	Praxis Hr. Dr. D. Rautenberg	Lüneburger Str. 17	21073	Hamburg	GERMANY
18	Praxis Hr. Dr. Karl-Heinz Belling	Frauenarztpraxis Schönstraße 9-10	13086	Berlin	GERMANY
19	Praxis Hr. Dr. K. Peters	Berner Herweg 157	22159	Hamburg	GERMANY
20	Praxis Hr. Dr. P. Schwaner	Montabaurerstr. 31	65936	Frankfurt	GERMANY
21	Praxis Hr. Dr. R. Etzrodt	Laasenerstr. 13	07545	Gera	GERMANY
22	Praxis Hr. Dr. R. Kuett	Frauenarztpraxis Mommsenstraße 22	90491	Nürnberg	GERMANY
23	Praxis Hr. Dr. U. Kopprasch	Frauenarztpraxis Amalie-Dietrich-Platz 5	01169	Dresden	GERMANY
24	Praxis Hr. Dr. Werner Göttker-Schnetmann	Eschersheimer Landstr. 41	60322	Frankfurt	GERMANY
25	Praxis Hr. H. Thelen	Rosa-Luxemburg-Str. 73	06917	Jessen	GERMANY
26	Praxis Hr. Prof. Dr. H.-J. Ahrendt	Halberstädter Strasse 122	39126	Magdeburg	GERMANY
27	Praxis Hr. R. Wähnert	Frauenarztpraxis Leipziger Str. 22	07545	Gera	GERMANY