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 Pharmaceutical Inc.	
Study Number:	91450 (308683)	NCT00266032
Study Phase:	III	
Official Study Title:	A multicenter, open, randomized, parallel-group comparison to assess the safety and efficacy of the oral contraceptive SH T00186D (0.02 mg ethinylestradiol as betadex clathrate and 3 mg drospirenone) in two variations of an extended regimen vs a standard regimen (24 + 4 days) in 1122 healthy female volunteers for one year, followed by a one-year safety extension	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EE20/DRSP (YAZ, BAY86-5300)	
Name of Active Ingredient:	Ethinylestradiol (EE) as betadex clathrate (β-CDC) and drospirenone (DRSP)	
Dose and Mode of Administration:	Treatment Phase 1 Group A ▪ 3 cycles of treatment, each cycle comprising of 120 days intended treatment with 1 tablet daily of SH T00186D followed by a 4-day tablet-free interval. ▪ If 3 consecutive days of bleeding and/or spotting occurred during the 120-day treatment period, a 4-day tablet-free interval was advised. ▪ The minimum period between 2 tablet-free intervals was 24 days. ▪ After each 4-day tablet-free interval, a new 120-day intended treatment period was to be restarted, resulting in a minimum of 3 and maximum of 13 withdrawal bleeding episodes during 1 year of treatment. Group B ▪ 3 cycles of treatment, each cycle comprising of 120 days uninterrupted treatment with 1 tablet daily of SH T00186D followed by a 4-day tablet-free interval. ▪ 3 withdrawal bleeding episodes during 1 year of treatment were expected. Group C ▪ Thirteen cycles of treatment, each cycle comprising of an intake of one tablet daily with 24 days of active tablets (SH T00186D) followed by 4 days of placebo tablets. ▪ Thirteen withdrawal bleeding episodes during one year of treatment were expected. Treatment Phase 2 Subjects after completing the 1-year treatment phase 1 entered into treatment phase 2. All subjects (except for those in the subgroup analyses of groups B and C) received treatment with the flexible extended regimen in treatment phase 2.	

	Mode of administration: Oral	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Approximately one year, followed by a one-year safety extension.	
Studied period:	Date of first subjects' first visit:	14 DEC 2005
	Date of last subjects' last visit:	28 OCT 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 11 DEC 2006) specified the following changes: • Defining end of study: A definition for the end of study was provided in accordance with the EU directive 2001/20/EC (end of the study was defined as the last subject's last visit). • Procedural change for bone mineral density (BMD)/bone markers subgroup: Subjects in the subgroup assessed for BMD and bone markers who completed Phase 1 and proceeded into Phase 2 of the study, were to continue with their respective treatment regimen (i.e., Groups B or C); all other subjects were to be treated as Group A. Other assessments, including taking a further endometrial biopsy, were to be performed on subjects of subgroups 1 and 2. • Secondary efficacy variable changed to co-primary efficacy variable: The number of unintended pregnancies (Pearl index and life table analysis), previously a secondary efficacy variable, was made co-primary efficacy variable in accordance with the FDA's recommendation during a scientific advisory meeting. Amendment no. 2 (dated 22 NOV 2007) specified the following modification: • Assessment of endometrial histology adjusted: To avoid inconsistencies in laboratory reports with respect to the frequency of glands, the histological assessment of endometrial tissue was adjusted.	
Study Centre(s):	The study was conducted at 37 centers in 3 different countries: Germany (30), Canada (6), the Netherlands (1).	
Methodology:	This multi-center, open, randomized, parallel group study was performed in 2 phases. Treatment Phase 1: After completion of all screening visit evaluations, subjects who were eligible to participate were randomly assigned to one of 3 treatment groups: A, B or C. ▪ Treatment Group A: Flexible extended regimen "managed bleeding" ▪ Treatment Group B: Fixed extended regimen ▪ Treatment Group C: Standard regimen Subgroup assessments for BMD, metabolic effects, endometrial response, ovarian morphology, and pharmacokinetics were carried out at 2 centers. Before starting study medication, "wash-out" of sex	

	hormones from any previous hormonal contraceptive for a period of 2 months (corresponding to 2 menstrual cycles) was required for subjects in the subgroups (selected from group A, B, and C) assessed for metabolic parameters, hormones, and biopsies. Treatment Phase 2: Subjects completing the 1-year treatment for phase 1 were offered a further year of treatment, i.e., treatment phase 2 in a mono-arm study with the flexible extended regimen for treatment group A. Subjects in the subgroup assessed for BMD and bone markers who completed Phase 1 and proceeded into Phase 2 of the study, however continued with their respective treatment regimen (i.e., groups B or C). Safety parameters (adverse events (AEs), general physical and gynecological examination, vital signs and safety laboratory) were assessed. Additional endometrial biopsies were obtained from subjects of subgroups 1 and 2, and further assessments were made in the BMD/bone markers subgroup.
Indication/ Main Inclusion Criteria:	Indication: Oral contraception Main Inclusion Criteria: Healthy female subjects; ≥18 and ≤35 years of age requesting contraception; smokers ≤30 years of age at screening
Study Objectives:	Overall: The objective of this study was to evaluate the safety and efficacy of SH T00186D in 2 variations of an extended regimen compared to the standard 24 + 4 day regimen administered in healthy female subjects between 18 and 35 years who requested contraceptive protection. Primary: Bleeding characteristics and contraceptive protection Secondary: Bleeding pattern, cycle control parameters, mean BMD loss and bone markers (subgroup only).
Evaluation Criteria:	Efficacy (Primary): • Total number of bleeding days in 1 year of 2 variations of an extended regimen • Number of observed unintended pregnancies (Pearl index and life table analyses) Efficacy (Secondary): • Bleeding pattern • Cycle control parameters • Mean BMD loss and bone markers (subgroup only) Efficacy (other): • Menstruation-related symptoms questionnaires, psychological general well-being index (PGWBI) (all groups) • Subject satisfaction with treatment (Groups A and B) Safety: • AEs

	• Endometrial characteristics (subgroup only): Histology, endometrial thickness and morphology (cysts) by Transvaginal Ultrasound (TVU) • Laboratory variables: ▪ Safety laboratory variables: Hematology, serum chemistry, liver enzymes, glycosylated hemoglobin (HbA1c), thyroid-stimulating hormone (TSH) and lipids ▪ Metabolic effects (subgroup only): Plasma lipids, hemostatic parameters, carbohydrate metabolism ▪ Hormone levels (subgroup only): Estradiol, Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Sex hormone binding globulin (SHBG) and testosterone • General physical and gynecological examination including cervical smear • Vital signs and body weight • Pregnancy tests
	Pharmacokinetics: • Population pharmacokinetics (PPK) • Pharmacokinetics of EE, DRSP, SHBG and corticosteroid-binding globulin (CBG) (subgroup only)
Statistical Methods:	Efficacy (Primary): The evaluation of the primary target variables was based on the full analysis set (FAS). A per-protocol set (PPS) analysis was done as well. The number of bleeding days per volunteer was calculated by summing up all days with bleeding intensity of spotting or worse. The primary evaluation was the comparison of groups A and C (hypothesis test) for this primary target variable, which was done for data within the 1st year of treatment only. The Pearl Index (PI) and the upper limit of the 95% confidence interval were calculated according to the EMEA Guideline Note for guidanceon clinical investigation of steroid contraceptives in women (adopted in JUL 2005). Additionally, an adjusted PI was calculated taking intake and absorption failure into account. Pregnancies with a conception date within the treatment-free interval (4 days) after the end of the study medication were also regarded as during treatment. The PI was changed to a co-primary endpoint based on the recommendation by the FDA during a Scientific Advice Meeting. As no further comparison or testing was done, no multiplicity issue arose. Efficacy (Secondary): Bleeding pattern indices, presence of expected bleeding, and cycle control were analyzed using descriptive statistics. The dichotomous variables were analyzed using descriptive statistics with numbers and percentages of observations in each category. The statistics were calculated for each cycle. A 95% CI for the difference of mean BMD loss was also calculated. Safety: Summary tables were provided for demographic, baseline and other safety data. Variables measured on metric scales were summarized by use of descriptive statistics. Variables measured on ordinal or nominal scales were summarized by use of frequency tables showing the number and percentage of subjects falling within a particular category. All AEs were presented in frequency tables for both subject count (number of subjects reporting AE) and event count (number of

	reported AEs). The frequency tables were based on classified data, and the classification was done according to Medical Dictionary for Regulatory Activities (MedDRA version 10.0) coding system.
	Pharmacokinetics : Pharmacokinetic data collected during the study were analyzed using non-linear mixed effects models. Mixed effects models or population-type pharmacokinetic models describe the relationship between dose and time and variables such as drug plasma concentrations. Both structural and random effects are involved in this relationship. A PPK compartmental model was developed using the concentration of the drug as the dependent variable.
Number of Subjects:	Planned: 1122 subjects (666 in Group A, 228 each in Groups B and C with a randomization ratio of 4:1:1 between group A, B and C except for the subjects of the subgroups for the investigation of BMD, endometrial safety and metabolic parameters who were equally randomized between the treatment groups). Analyzed: 1166 subjects; 691 randomized to Group A, 236 to Group B, and 239 to Group C.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 1312 subjects screened, 146 were screening failures. A total of 91.5% of all randomized subjects qualified for the FAS; there were no differences between the treatment groups. A total of 47.0% of all subjects were part of the PPS, a higher proportion of subjects in Group C (59.4%) and less in Group B (39.0%) compared with the overall mean. All major protocol deviations leading to exclusion from the PPS occurred in the category of treatment deviations and were related to the number of tablets taken per cycle, the cycle length and the tablet-free interval length.

All subjects were between 18 and 35 years old, the median was 24 years in all three treatment groups. The median overall height was 168 cm, the median weight 62.0 kg, and the median Body Mass Index (BMI) 22.1 kg/m^2. The overall mean age at menarche was 12.9 years Standard deviation (SD) 1.31 with no differences between the groups. Dysmenorrhea occurred with an overall incidence of 24.9%, amenorrhea with an incidence of 3.0%, and intracyclic vaginal bleeding with 4.9% at screening.

Overall 79.1% of all subjects had used oral contraceptives (OCs) at screening.

Results Summary — Efficacy

The primary efficacy variable, number of bleeding days within the first year of treatment (inclusive spotting), showed a clear statistically significant superiority of the flexible (extended) regimen (Treatment A) as compared to the standard 24+4 regimen (Treatment C). In FAS the mean number of bleeding days under the flexible (extended) treatment was 41 days (SD 29; n=640) versus 66 days (SD 27; n=215) under the standard regimen ($p<0.001$). Therefore the study objective was clearly achieved.

Treatment A was also superior to Treatment B: in Group B the mean number of bleeding days under the fixed extended regimen was 60.9 days (SD 51; n=209).

For the other primary efficacy variable, PI, an estimate of 0.64 (95% confidence interval [0.28; 1.26]) for flexible (extended) treatment was derived, based on pregnancies and 1253 women years of exposure. The adjusted PI was 0.60 (95% confidence interval [0.24 ; 1.24]) based on 1166 women years of exposure and 7 pregnancies, that occurred under tremanent and were assessed as method failure (i.e., a subject failure could not be confirmed). The PI was calculated only in Group A as the two other groups were too small for a reliable

calculation.

The secondary efficacy variables were bleeding pattern for all subjects and BMD with bone markers in a subgroup analysis.

Bleeding occurred more frequently in the standard regimen in Group C (consistently found in all reference periods, 90 and 120 days duration). The number of bleeding days (excluding spotting) was lower in Group A (20.8 days, SD 15.22, median 18.0 days) and B (23.8 days, SD 24.46, median 17.0 days) compared to Group C (43.4 days, SD 19.99, median 46.0 days). The proportion of bleeding days excluding spotting (of all days recorded on the diary cards) in the three groups was also in favour of Group A: 6.92% (SD 6.92, median 5.5%) and 9.94% (SD 13.10, median 5.7%) in Group B vs Group C 13.57% (SD 8.28, median 13.2%). The time to the first bleeding or spotting day was slightly longer in Group A (mean 70.6, SD 56.04, median 55.0 days) vs Group B (mean 64.4, SD 58.35, median 46.0 days). In Group B, the fixed extended regimen, a considerable number of spotting-only days occurred, especially early under treatment, while in Group A, there were less spotting-only days than under treatment in Group B and less bleeding and bleeding/spotting days than in Group C.

The mean length of withdrawal bleeding was longer in Group B (9.8 to 10.5 days per cycle, the values given are ranges over Cycles 1 to 2 – thereafter 12 or less subjects had withdrawal bleeding) than in Group A subjects (7.5 to 9.8 days, the values given are ranges over Cycles 1-9- thereafter 12 or less subjects had withdrawal bleeding). For Group C the mean length of withdrawal bleeding episodes was between 4.4 and 5.2 days per cycle. It should be understood that a "withdrawal bleeding episode" in Group A included a number of days with spotting/bleeding before the actual hormonal withdrawal. The regimen required 3 days of unscheduled bleedings before the woman should allow the 4-day break to induce withdrawal bleeding. In addition, it should be noted that Group C should not have had more than 3 cycles as it was a long-cycle regimen with a fixed cycle length of 124 days. All women in this group with more than 3 cycles took more breaks than allowed and thus violated the rules of the regimen.

Days with scheduled and unscheduled bleeding were evaluated for the flexible regimens only. Days with unscheduled bleeding/spotting were any bleeding days that occurred while taking active hormones regardless of the duration of the intake, unless they occurred after the tablet-free interval during days 1 - 4 of the subsequent treatment cycle, or unless they occurred during days 1 - 7 of the first treatment cycle. Days with scheduled bleeding were any bleeding/spotting days that occurred during the tablet-free interval, regardless of the duration of the tablet intake, or during the next 4 days of the subsequent treatment cycle.

The mean number of scheduled bleeding days was higher in Group A. The mean number of unscheduled bleeding days was 46.6 days (SD 48.4) during the one-year treatment period and by far higher compared to the mean of 17.1 (SD 17.4) days in Group B.

There were slight increases in BMD means and medians in lumbar spine and hip observed for the BMD-subgroup of Group B from baseline to treatment phase 1 and almost unchanged values described for the subgroup of Group C.

Osteocalcin levels decreased, mostly in the first half of treatment phase 1 until Week 27, and were 31.23 ng/mL (SD 10.335) in Group B in Week 3 and 22.45 ng/mL (SD 7.105) in Week 27. The time-points thereafter resembled the Week 27 measurement. Also in Group C there was a slight decrease from Week 3 with 26.39 ng/mL (SD 9.681) to Week 27 with 21.66 (SD 7.708). Later measurements were in the range of the Week 27 level. The mean bone alkaline phosphatase (AP) levels at baseline were 24.41 U/mL (SD 8.17) in Group B, and 21.20 U/mL (SD 6.32) in Group C subjects. Thereafter levels decreased in the two Groups B and C to an overall mean of 19.12 U/mL (SD 7.17) in Week 3, 16.91 U/mL (SD 7.10) in Week 27, and 17.99 U/mL (SD 7.00) in Week 51 of treatment phase 1. The mean Carboxy-terminal cross-linking telopeptide (CTX) levels decreased from baseline when they were 588.0 pg/mL (SD

226.92) in Group B, and 548.5 pg/mL (SD 245.99) in Group C subjects during treatment phase 1. Mean CTX levels were 362.0 pg/mL (SD 101.27) in Group B and 367.4 pg/mL (SD 141.24) in Group C subjects at Week 51 of treatment phase 1.

For the individual questions asking for the condition in the three months before the respective visit, there were remarkable improvements compared to baseline and differences observed after baseline in the three treatment groups as revealed in a menstruation-related symptoms questionnaire. Much of the difference was due to the differences in regimen, leading to extended cycles meaning absence of menstrual bleeding events. Answers in Week 11 in Group C resembled the values at baseline in the FAS with 86.1% having a menstrual bleeding duration of 3 to 7 days and a cycle length of 21 to 28 days in 76.6% of all Group C subjects. In contrast, in Group A the information about duration and cycle length was missing for 51.9% and 52.2% of the subjects; in Group B 59.7% and 62.2% had missing information due to the absence of withdrawal bleeding. While 0.5% of the Group C subjects had a cycle of more than 35 days, this was true for 24.4% of Group A and 11.2% of the Group B subjects in Week 11. While heavy bleeding was present at 1 to 3 days per cycle at baseline in overall more than 60% of all subjects, it decreased with treatment in all treatment groups, namely in Week 11 it occurred in 12.3% of Group A subjects, in 9.2% subjects in Group B and 25.8% in Group C. Overall 44.0% had mild abdominal/pelvic pain at baseline. Occurrence of mild pain decreased with treatment and in Week 11 it occurred in 14.5%, 8.2% and 28.7% of the Group A, B, and C subjects, respectively. A total of 25.5% had backache at baseline and decreased in all three treatment groups with treatment: 8.4% of Group A, 5.1% of Group B, and 13.9% of Group C had backache at Week 11. About 10% had impaired daily activities at baseline due to the menstruation-related symptoms. At Week 11 this proportion had decreased with treatment to 2.3% in Group A, 0.0% in Group B, and 3.3% in Group C.

Similarly, also the subject's satisfaction questionnaire confirmed the overall satisfaction with study treatment. For example, of the subjects with painful menstruations present at baseline, an improvement in frequency was observed in 77.1% in Group A, 81.4% in Group B, and 77.8% in Group C. "Very satisfied" with the long-term regimen were 62.0% in Group A and 58.1% in Group B, "quite satisfied" were 33.5% of the Group A subjects and 32.6% of the Group B. Regarding the likelihood that they would switch to the long-term OC regimen, "very probable" was the response in 51.4% of the Group A subjects and 46.5% of the Group B subjects, "quite probable" was chosen by 34.1% of Group A and 25.6% of Group B. Consequently, 86.0% of the Group A and 79.1% of the Group B subjects stated to recommend the long-term OC regimen to a friend.

The PGWBI showed a small decrease of the total score in all three groups of overall 1.18 (SD 11.70, change from baseline at Week 27) from the baseline overall mean of 109.3. In Week 51 the change from baseline was minimal with an "increase" of 0.05 (SD 12.47).

Results Summary — Safety

Adverse Events:
Overall, in the course of the study, there were 3531 AEs in 790 subjects (74.0%, ie. 1955 AEs in 465 (72.4%) Group A subjects, 772 AEs in 157 (75.1%) Group B subjects, and 804 AEs in 168 (77.8%) Group C subjects. The three most frequent AEs were nasopharyngitis, headache, and diarrhea. Headache was slightly less frequent in Group A subjects, and cystitis was slightly more frequent in Group B compared to the other treatment groups. Other than that, overall and AE specific frequencies did not differ between the treatment groups in this study. The majority of subjects with AEs had AEs that were assessed by the investigator as not related to the study drug; over 90% were mild or moderate in intensity. There were no differences between the groups in the maximum degree of study-drug relatedness of the AE. About 90% of all AEs did not require a study drug action and resolved by the end of the treatment phase.
No deaths were reported during this study.

A total of 35 serious adverse events (SAEs) occurred in 29 subjects (2.7% of all subjects),

i.e., 19 SAEs in 3.0% of all Group A subjects, 9 SAEs in 3.3% of all Group B, and 3 SAEs in 1.4% of all Group C subjects. Abdominal pain (in 2 Group A subjects) and ovarian cyst (1 subject in Group A and B each) were the only SAEs occurring more than once. The investigator assessed the SAEs as study drug-related in a total of 3 subjects (0.3% of all subjects, or 10.3% of all subjects with SAEs); all 3 cases occurred in Group A (15.8% of all subjects in this group with SAEs). All 3 were possibly related to the study drug. One subject had an SAE in the MedDRA sytem organ class (SOC) "neoplasms benign, malignant, and unspecified"; MedDRA preferred term (PT) was "focal nodular hyperplasia". Another subject had an SAE in the SOC "neoplasms benign, malignant, and unspecified"; PT was "uterine leiomyoma". The subjects discontinued the study medication due to this SAE. One of the subjects had an SAE in the SOC "vascular disorders"; PT was "deep vein thrombosis".

Seventy-eight (6.7% of a total of 1166) subjects discontinued the study during treatment phase 1 and 9 (1.1% of the remaining 783 subjects) in phase 2. The highest proportion of subjects discontinuing the study in phase 1 due to an AE was observed in Group B (11.0%), followed by Group A (6.1%), and then Group C (4.2%). Occurrences in phase 2 were rarer and between 0% and 2.4%.

Other safety:
None of the laboratory parameters or physical or gynecological examination findings gave rise to any concern.

An analysis of metabolic effects, hormone levels, and endometrial characteristics was done in a subgroup. These women had to allow a wash-out of sex hormones for a period of 2 months (corresponding to 2 menstrual cycles) before starting study medication. Similar trends were shown for all three treatments in this subgroup for metabolic effects during a glucose tolerance test, hemostatic parameters, plasma lipids and hormone levels. As expected estradiol, FSH, LH, and testosterone levels decreased compared to baseline while SHBG increased under treatment with the OC in all 3 regimen.

All endometrial biopsy findings were normal. The endometrium was characterized at the end of treatment phase 1 in 23 Group A and 17 Group B subjects and again after treatment phase 2 in 7 Group A and 9 Group B subjects. Most had an inactive (30.4% of Group A, 17.6% of Group B), atrophic (26.1% of Group A, 29.4% of Group B), or secretory endometrium of the progestational type (21.7% of Group A and 23.5% of Group B) at the end of treatment phase 1. Weakly proliferative endometrium occurred in 17.4% of Group A subjects and 17.6% of Group B subjects. After treatment phase 2 atrophic (57.1% of Group A, 0.0% of Group B) and secretory endometrium of the progestational type (14.3% of Group A and 44.4% of Group B) were the most frequent types.

Results Summary — Pharmacokinetics

The pharmacokinetics of drospirenone and ethinylestradiol could be adequately described using sparse sample collection and by means of a population pharmacokinetic approach. No clinically relevant changes in the pharmacokinetics of drospirenone and ethinylestradiol were observed over time. Exposures of drospirenone and ethinylestradiol were comparable between treatment groups. Body weight and age were found to significantly impact the pharmacokinetics of drospirenone (weight) and ethinylestradiol (weight and age) but the overall changes in drug exposures were small (below 20%) and not considered to be clinically relevant.

Conclusion(s)			
In this study, the safety profiles of all three applied treatments were comparable to the known OC safety profiles. The PI was calculated in Group A only as the two other groups were too small for a reliable calculation. The PI of 0.64 was as good as expected. Treatment A, the flexible extended regimen for managed bleeding, had a more favorable effect on bleeding pattern with less days of bleeding per year compared to the standard regimen of Group C and the fixed extended regimen of Group B. In comparison to the fixed extended regimen, the reduction of days with unscheduled bleeding is an additional advantage of the flexible extended regimen. The possibility to treat an unscheduled bleeding episode during the flexible intake phase with the hormonal withdrawal of the 4-day break provides a schedule to the woman as it transforms the breakthrough bleeding into a withdrawal bleeding with an expected length of approximately 5 days.			
Publication(s):	Klipping C, Duijkers I, Fortier MP, Marr J, Trummer D, Elliesen J. Long-term tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: results from a randomised, controlled, multicentre study. J Fam Plann Reprod Health Care. 2012 Apr;38(2):84-93. Klipping C, Duijkers I, Fortier MP, Marr J, Trummer D, Elliesen J. Contraceptive efficacy and tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study. J Fam Plann Reprod Health Care. 2012 Apr;38(2):73-83.		
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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	Centre d'étude clinique de Montréal Inc.	5554 rue St-Zotique Est App. 1	H1T 1P6	Montreal	CANADA
2	Clinique de Gynecologie	1785 avenue St-Marc Suite 304	G9N 2H6	Shawinigan	CANADA
3	Clinique Médicale des Campus	2880 Quatre-Bourgeois Suite 115	G1V 4X7	Ste-Foy	CANADA
4	Clinique Recherche en Sante des Femmes Inc.	1000 Chemin Ste-Foy Suite 102	G1S 2L6	Quebec	CANADA
5	Kells Medical Research Group, Inc.	175 Stillview Suite 106	H9R 4S3	Pointe-Claire	CANADA
6	Rhodin Recherche Clinique	609 Lindsay	J2B 1H8	Drummondville	CANADA
7	Dinox GmbH Berlin	Anklamer Str. 38	10115	Berlin	GERMANY
8	Frauenarztpraxis Dr. med. Gabriele Weinreich	Friedrich-Engels-Strasse 2	39130	Magdeburg	GERMANY

9	Frauenarztpraxis Dr. med. Wolfram Brach	Am Stadtbrunnen 8 - 10	63128	Dietzenbach	GERMANY
10	Frauenarztpraxis Hr. Dr. B. Hamann	Wollankstrasse 11	13187	Berlin	GERMANY
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13	Kreiskrankenhaus Krumbach	Mindelheimerstr. 69	86381	Krumbach	GERMANY
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16	Praxis Fr. A. Heweker	Steinstrasse 6a	06406	Bernburg	GERMANY
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18	Praxis Fr. Dr. A.Mönch-Hering	Frauenarztpraxis Bahnhofstr. 25	07768	Kahla	GERMANY
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20	Praxis Fr. Dr. J. Tyagi	Mozartstr. 2	63165	Mühlheim	GERMANY
21	Praxis Fr. Dr. S. Krepler	Erlanger Allee 103	07747	Jena	GERMANY
22	Praxis Fr. I. Gröger	Schillerstr. 44	04808	Wurzen	GERMANY
23	Praxis Hr. Dr. A. Soder	Zehntwiesenstr. 5	76275	Ettlingen	GERMANY
24	Praxis Hr. Dr. D. Rautenberg	Lüneburger Str. 17	21073	Hamburg	GERMANY
25	Praxis Hr. Dr. H. Frommeyer	Johannisstrasse 111	49074	Osnabrück	GERMANY
26	Praxis Hr. Dr. H. Zabel	Rathausplatz 11/12	37120	Bovenden	GERMANY
27	Praxis Hr. Dr. K. Greven	Pfarrstr. 47	30459	Hannover	GERMANY

28	Praxis Hr. Dr. L. Weihe	Platenstr. 15	91522	Ansbach	GERMANY
29	Praxis Hr. Dr. P. Schwaner	Montabaurerstr. 31	65936	Frankfurt	GERMANY
30	Praxis Hr. Dr. R. Etzrodt	Laasenerstr. 13	07545	Gera	GERMANY
31	Praxis Hr. Dr. R. Kuett	Frauenarztpraxis Mommsenstraße 22	90491	Nürnberg	GERMANY
32	Praxis Hr. Dr. U. Kohoutek	Diakonissenstrasse 1	76199	Karlsruhe	GERMANY
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34	Praxis Hr. H. Thelen	Rosa-Luxemburg-Str. 73	06917	Jessen	GERMANY
35	Praxis Hr. Prof. Dr. H.-J. Ahrendt	Halberstädter Strasse 122	39126	Magdeburg	GERMANY
36	Praxis Hr. R. Wähnert	Frauenarztpraxis Leipziger Str. 22	07545	Gera	GERMANY
37	Dinox B.V.	DINOX B.V. Hanzeplein 1, Entrance 53 9713 GZ Groningen	9713 GZ	Groningen	NETHERLANDS

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	YAZ
Brand/Trade Name(s) ex-US	YAZ, Dschess, Dzhes, Dzhess, Eloine, Ethinylestradiol/Drospirenon 24+4, Ethinylestradiol/Drospirenone, Leah, Linatera, Rimendia, Yasmin 24/4, Yasminiq, Yaz 24+4, YAZZ 24+4, Yvette
Generic Name	Drospirenone; Ethinylestradiol
Main Product Company Code	BAY86-5300
Other Company Code(s)	SH T 186 DF
Chemical Description	Drospirenone: 6ß,7ß;15ß,16ß-Dimethylene-3-oxo-17alpha-pregn-4-ene-21,17-carbolactone Ethinylestradiol: 17 alpha-Ethynyl-1,3,5(10)-estratriene-3,17 ß-diol
Other Product Aliases	Yasmin 20

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